ANTICIPATE and COMMUNICATE

Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts

Presidential Commission *for the* Study of Bioethical Issues

December 2013

On the cover: Image* of a biopsy of an adenoma, or benign tumor, in the pituitary gland of the brain as seen through a microscope. Such a finding can originate incidentally via a number of diagnostic imaging tools. High resolution imaging can reveal an incidental pituitary tumor 10 percent of the time; these tumors are usually small and asymptomatic.

Source: Aron, D.C., and T.A. Howlett. (2000). Pituitary incidentalomas. *Endocrinology and Metabolism Clinics of North America*, 29(1), 205-221.

*Adaptation of original.

Credit: Biophoto Associates / Science Source

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Presidential Commission
***for the* Study of Bioethical Issues**

Washington, D.C.
December 2013

http://www.bioethics.gov

ABOUT THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

The Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) is an advisory panel of the nation's leaders in medicine, science, ethics, religion, law, and engineering. The Bioethics Commission advises the President on bioethical issues arising from advances in biomedicine and related areas of science and technology. The Bioethics Commission seeks to identify and promote policies and practices that ensure scientific research, health care delivery, and technological innovation are conducted in a socially and ethically responsible manner.

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CONTENTS

Presidential Commission for the Study of Bioethical Issues

President Barack Obama
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Mr. President:

On behalf of the Presidential Commission for the Study of Bioethical Issues, we present to you *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*. In this report the Bioethics Commission focuses on the distinct ethical issues concerning the management of incidental and secondary findings that arise from clinical, research, and direct-to-consumer testing. Incidental findings traditionally are defined as results that arise that are outside the original purpose for which a diagnostic test or procedure was conducted. Such findings can be lifesaving, but also can lead to uncertainty and distress if they are unexpected or identify conditions for which no effective treatment is available.

Building on its past work in *Privacy and Progress in Whole Genome Sequencing*, released in October 2012, the Bioethics Commission held four public meetings regarding incidental findings and heard from speakers with diverse backgrounds and perspectives. The Bioethics Commission also solicited public comment and received many thoughtful responses.

As technology advances, the likelihood of discovering incidental and secondary findings is expected to increase. The Bioethics Commission believes that a number of ethical principles can guide clinicians, researchers, and direct-to-consumer companies in developing sound policies for the ethical management of such findings. The Bioethics Commission therefore offers 17 recommendations to guide practitioners across testing modalities and health care settings.

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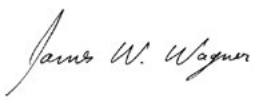
The Bioethics Commission recommends that all practitioners should anticipate and plan for incidental and secondary findings to the best of their ability in order to provide as much information as possible to guide recipient decision making. Potential recipients should be fully informed about the possibility of incidental and secondary findings before any tests are conducted. To aid in this process, professional organizations and experts should continue to enumerate all *anticipatable* findings and guidance about their ethical management.

The Bioethics Commission is honored by the trust you have placed in us and we are grateful for the opportunity to serve you and the nation in this way.

Sincerely,

Amy Gutmann, Ph.D.
Chair



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The Bioethics Commission is indebted to those who contributed their wisdom, time, and energy to this report. It offers special thanks to the diverse group of outstanding speakers who shared their expertise and personal experiences, and engaged in productive and thought-provoking discussions at its public meetings.

The Bioethics Commission is also grateful to its talented and capable staff for their unflagging support, careful research, and considerable insights on the ethics of managing incidental and secondary findings in the clinical, research, and direct-to-consumer settings. The Bioethics Commission extends particular thanks to Executive Director Lisa M. Lee for her steadfast leadership and unwavering commitment to the Bioethics Commission's work and to Senior Advisor Paul Lombardo for his expert review. The Bioethics Commission also appreciates the work of Associate Director Kayte Spector-Bagdady and staff lead Elizabeth Pike, whose diligence and constant efforts ensured a nuanced review of this critical topic.

EXECUTIVE SUMMARY

A healthy young medical student participated in research using functional magnetic resonance imaging to look at brain activity while doing a memory test. During this brain scan, the researcher noticed a concerning mass. The student rushed to the hospital for further examination, which was followed by successful treatment of the incidental finding that she credits with saving her life.[1]

Two years later, a different woman collapsed from over-hydration while running a marathon. During an evaluation, her emergency care team discovered a small brain tumor. She opted, in consultation with her physicians, for a watch-and-wait approach, monitoring the tumor for changes before making any treatment decisions. She has been watching anxiously for almost 10 years, even though the tumor might never affect her health.[2]

Incidental findings—traditionally defined as results that arise that are outside the original purpose for which the test or procedure was conducted[3]—can create a range of practical, legal, and ethical challenges for recipients and practitioners. Discovering an incidental finding can be lifesaving, but it also can lead to uncertainty and distress without any corresponding improvement in health or wellbeing. For incidental findings of unknown significance, conducting additional follow-up tests or procedures can be risky and costly.[4] Moreover, there is tremendous variation among potential recipients about whether, when, and how they would choose to have incidental findings disclosed. Information that one recipient regards as an unnecessary cause of anxiety could lead another recipient to feel empowered in making health-related decisions.

The increasing technological capability of the modalities discussed in this chapter leads to an increased likelihood of discovering incidental and secondary findings. The movement from discrete tests toward large-scale genetic sequencing increases the likelihood that clinicians, researchers, and direct-to-consumer (DTC) providers will confront the issue of incidental and secondary findings. And as payment structures evolve so that bundled tests are presumed to be more cost effective than discrete tests, the number of unintended findings is expected to increase.

In this report, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer*

Contexts, the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) focuses on the distinct ethical issues concerning incidental and secondary findings that arise from various modalities—including large-scale genetic sequencing, testing of biological specimens, and imaging—in contexts that include the clinic, research, and DTC testing. Because the term "incidental findings" as traditionally used can limit consideration of critical ethical issues, the Bioethics Commission considers several types of ethically challenging findings, including incidental, secondary, and discovery findings.

For purposes of this report, the Bioethics Commission divides the term "incidental finding" into two categories: incidental findings that are "anticipatable" and those that are "unanticipatable." An *anticipatable incidental finding* is a finding that is known to be associated with a test or procedure. An *unanticipatable incidental finding* includes a finding that could not have been anticipated given the current state of scientific knowledge. A *secondary finding* refers to a finding that is actively sought by a practitioner that is not the primary target. A *discovery finding* refers to the results of a broad or wide-ranging test that was intended to reveal anything of interest. This report focuses primarily on anticipatable and unanticipatable incidental findings as well as secondary findings. For simplicity, the generic term "incidental finding" is used in reference to both anticipatable and unanticipatable incidental findings; distinctions are made as necessary and relevant.

In its previous report, *Privacy and Progress in Whole Genome Sequencing*, the Bioethics Commission addressed incidental findings with regard to large-scale genetic sequencing.[5] A more thorough deliberation about the ethical obligations of clinicians, researchers, and DTC providers, as well as consideration of the incidental findings that arise from various diagnostic modalities, is the goal of this report, which makes 17 recommendations to guide practitioners across modalities and settings.

The current challenge for public policy and professional ethics is to identify through thoughtful deliberation specific criteria that practitioners can use to determine when it is ethically permissible or obligatory for clinicians, researchers, or DTC companies to disclose and not disclose incidental findings to patients, participants, or consumers. The technical aspects of managing the response to incidental findings—including the circumstances under which

practitioners should return particular findings—is best carried out by those with the relevant expertise to make those nuanced determinations. In contrast to developing detailed prescriptions for practice, the Bioethics Commission aims through this report to provide a broad ethical analysis of the principles, virtues, and duties relevant to managing incidental and secondary findings to ground these determinations.

ETHICAL BASIS OF THE MANAGEMENT OF INCIDENTAL AND SECONDARY FINDINGS

Longstanding ethical principles ground the Bioethics Commission's consideration of incidental and secondary findings. In seeking to create mutually acceptable and justifiable public policy, a process of democratic deliberation can lead citizens, policy makers, and experts to identify common ground and compromise.[6] Because professionals in a variety of contexts can encounter incidental and secondary findings, guidance must appeal to principles that bridge these contexts. The interpretation, application, scope, strength, and stringency of each principle, however, can vary among and within each context.

The Bioethics Commission found four ethical principles to be particularly applicable to the ethical assessment of incidental and secondary findings: respect for persons, beneficence, justice and fairness, and intellectual freedom and responsibility. The principle of respect for persons recognizes the fundamental human capacity for rational self-determination—the autonomous ability to identify personal preferences, act on these desires, and direct the course of one's life. The principle of beneficence calls on professionals to take actions to ensure the wellbeing of others, while its corollary non-maleficence requires not imposing harms on others. The principle of justice and fairness requires fair and equitable treatment of all. Finally, the principle of intellectual freedom and responsibility protects sustained and dedicated creative intellectual exploration that furthers scientific progress, while requiring that practitioners take responsibility for their actions. A context-specific interpretation of each principle is necessary to translate the principles into actionable guidance,[7] and is undertaken in each of the context-specific chapters that follow.

RECOMMENDATIONS

In this report, the Bioethics Commission makes two types of recommendations: those applicable to the ethical management of incidental and secondary findings across contexts, and those most relevant in specific settings or situations. The following section provides an overview of these recommendations.

Overarching Recommendations

Although many ethical considerations concerning the management of incidental and secondary findings are specific to the setting in which they occur—and the type of relationship between the practitioner and the potential recipient—there are several important considerations applicable to these findings in *all* contexts. The Bioethics Commission thus offers five overarching recommendations.

Overarching Recommendations

Informing Persons Tested
Evidence-Based Practice Guidelines
Additional Empirical Research
Educating Stakeholders
Justice and Fairness and Health Inequities

Informing Persons Tested

In all contexts, potential recipients of incidental and secondary findings—patients, research participants, and consumers—should be informed about the likelihood of such findings arising from a particular test or procedure. Providing this information enables a potential recipient to make an autonomous decision about whether and how to proceed. This disclosure also allows practitioners to anticipate and think through the consequences of conducting various tests and procedures. Open communication between practitioners and individuals, accessible and understandable documents and resources, and transparent processes in all three contexts help ensure that individuals understand risks and benefits before they consent.

Recommendation 1

Clinicians, researchers, and direct-to-consumer providers should describe to potential recipients incidental and secondary findings that are likely to arise or be sought from the tests and procedures conducted. Practitioners should inform potential recipients about their plan for disclosing and managing incidental and secondary findings, including what findings will and will not be returned.

Practitioners should facilitate and work to improve the process of informed consent in all contexts. Adequately informing individuals about the potential for discovering incidental findings should include an explanation of the nature of anticipatable incidental findings, as well as the possibility of discovering unanticipatable incidental findings, and a thorough description of any secondary findings that will be sought.

Evidence-Based Practice Guidelines

Practice guidelines can inform practitioners about the anticipatable incidental findings likely to arise during common tests and procedures, and the ways in which practitioners can best manage these findings—including the possibility of actively seeking particular findings as secondary findings. Guidelines tailored to each modality, procedure, or test that address the findings likely to arise in each context can help practitioners develop their own ethically sound policies for managing such findings.

Recommendation 2

Professional representative groups should develop guidelines that categorize the findings likely to arise from each diagnostic modality; develop best practices for managing incidental and secondary findings; and share these guidelines among practitioners in the clinical, research, and direct-to-consumer contexts.

Professional and institutional guidelines are crucial to ensuring consistent and systematic categorization, disclosure, and management of incidental and secondary findings. In developing guidelines, professional organizations should employ a variety of criteria, including clinical significance and actionability, and should also take into account the economic costs associated with conducting additional diagnostic tests in relation to ascertainable benefits.

As professional organizations increasingly recognize certain anticipatable findings likely to arise from particular tests and procedures, and determine that certain findings are sufficiently significant and actionable to merit disclosure, a number of findings—previously considered anticipatable incidental findings—are likely to become actively sought secondary findings. The transition from unanticipated incidental findings to anticipated or

secondary findings allows for more information to be provided to potential recipients and therefore facilitates more meaningful consent across contexts.

Additional Empirical Research

Additional empirical research and scholarship is needed concerning the discovery, disclosure, and management of incidental and secondary findings. In its report, *Privacy and Progress in Whole Genome Sequencing*, the Bioethics Commission recommended that funders of whole genome sequencing research conduct further studies to evaluate proposed frameworks for offering to return incidental findings and other research results.[8] The Bioethics Commission continues to believe that additional empirical data are critical to informing the ethical management of incidental and secondary findings, and therefore suggests expanding the scope of such recommended empirical research.

Recommendation 3

Federal agencies and other interested parties should continue to fund research regarding incidental and secondary findings. This research should consider the types and frequency of findings that can arise from various modalities; the potential costs, benefits, and harms of identifying, disclosing, and managing these findings; and recipient and practitioner preferences about the discovery, disclosure, and management of incidental and secondary findings.

Data about incidental and secondary findings can come from a variety of sources. One potential source is practitioners gathering information about incidental and secondary findings through their work, monitoring findings that arise, and developing databases about the disclosure and management of such findings.[9] Professional societies also can address specific questions about findings likely to arise from various modalities and in various contexts, and the professional skills or training necessary to interpret and manage these findings.[10]

Educating Stakeholders

Educating the public about incidental and secondary findings enables those undergoing tests or procedures to make better informed decisions and develop informed preferences about receiving potential findings. Educating practitioners about their ethical obligations enables them to make more

thoughtful decisions about how to anticipate, disclose, and manage incidental and secondary findings.

Recommendation 4

Public and private entities should prepare educational materials to inform all stakeholders—including practitioners, institutional review boards, and potential recipients—about the ethical, practical, and legal considerations raised by incidental and secondary findings.

In addition to the educational efforts of the Bioethics Commission, a wide variety of groups, governmental bodies, and professional organizations can assist in educating stakeholders about incidental and secondary findings. For example, public and private entities tasked with providing education about and regulation of medical research can bolster existing materials to better address the ethical issues raised by incidental and secondary findings.

Justice and Fairness and Health Inequities

Justice and fairness in health care requires that all individuals have access to adequate affordable services to meet basic health care needs. Our society should continue to seek cost-effective ways to provide affordable access to health care to as many individuals as possible. The right test at the right time can be lifesaving, while over-testing comes with its own risks that can be detrimental to both mental and physical health. Adequate, affordable care provides the backdrop against which competent health care professionals can offer expert advice, personalized counseling, and follow-up care to harness the benefits of these developing diagnostic technologies. Coupling counseling and guidance with new technologies can help patients and their practitioners make meaningful decisions about turning medical information into actionable clinical knowledge in accordance with personal health care preferences and values.[11] Currently, however, many persons lack access to such services. The principle of justice and fairness suggests finding affordable, cost-effective ways to give all people in need access to informed counseling and related medical care.

Recommendation 5

The principle of justice and fairness requires that all individuals have access to adequate information, guidance, and support in making informed choices about what medical tests to undergo, what kind of information to seek, and what to do with information once received. The principle of justice and fairness also requires affordable access to quality information about incidental and secondary findings, before and after testing, which when coupled with access to care can be potentially lifesaving or life enhancing.

For incidental findings to be managed in an appropriate and ethical way, there must be a health care system available to all that is capable of dealing with medically significant findings, whether discovered incidentally or as primary or secondary findings. This includes support for time afforded to practitioners to discuss with potential recipients how incidental and secondary findings will be handled.

Context-Specific Recommendations

The overarching recommendations listed above provide guidance for the ethical management of incidental and secondary findings across contexts. However, given the differences among the clinical, research, and DTC settings, the Bioethics Commission also sought to provide specific guidance for practitioners in each context regarding the ethical management of incidental and secondary findings.

Clinical Recommendations

When clinicians discover incidental findings, or contemplate seeking secondary findings, their professional judgment must include skilled and insightful deliberation guided by ethical principles including respect for persons, beneficence, and justice and fairness. Application of these principles

to incidental and secondary findings in the clinical context leads to the following recommendations.

Consent in the Clinical Context

A primary point of communication between clinicians and patients occurs during the clinical informed consent process, ideally led by the clinician most intimately familiar with the intervention and its possible consequences.[12] As part of the consent process, clinicians should alert patients that a particular test or procedure could or will give rise to anticipatable incidental and secondary findings. Clinicians should also notify patients about the possibility that unanticipatable findings could arise that could lead to additional diagnostic testing or clinical care. The patient should be encouraged to ask questions, state reservations, and express preferences about the return and management of incidental and secondary findings.

Recommendation 6

Clinicians should make patients aware that incidental and secondary findings are a possible, or likely, result of the tests or procedures being conducted. Clinicians should engage in shared decision making with patients about the scope of findings that will be communicated and the steps to be taken upon discovery of incidental findings. Clinicians should respect a patient's preference not to know about incidental or secondary findings to the extent consistent with the clinician's fiduciary duty.

There are multiple points at which a clinician's ability to communicate clearly and effectively about incidental and secondary findings is important. Clinicians should alert patients to the possibility of discovering incidental findings, and any secondary findings that will be actively sought, *before* testing occurs so that patients have the opportunity to express preferences regarding their disclosure and subsequent management.

With the increasing emphasis on patient autonomy and shared decision making, it is important to employ effective methods of conveying information about risk.[13] Clinicians can facilitate patient understanding by effectively presenting pertinent facts and data. In approaching shared decision making in the clinical setting, clinicians must be aware of factors that shape patients' perceptions of risk in order to communicate effectively. Clinicians should give patients enough information so that they comprehend their options,

and should also protect patients from unnecessary anxiety produced by misunderstood communication of risk.

Recommendation 7

In communicating difficult to understand information about incidental and secondary findings, clinicians should consider providing patients with decision aids and graphical representations, using population-based evidence, and describing a patient's absolute risk (the chance of any person getting a disease) rather than or in addition to relative risk (whether a person's chance is higher or lower than another's).

Accurate graphical displays of numerical and probabilistic health information can assist patients in accessing, processing, interpreting, and acting on numerical health information.[14] It is also critical that clinicians use relevant and understandable numerical evidence to support shared decision making. When appropriate, numeric assessments of risk should be provided as absolute risk instead of or in addition to relative risk, as relative risk can be easily misinterpreted. Similarly, population-based evidence can help patients understand their overall risk compared with the population as a whole.

Empirical Data in the Clinical Context

Little is known about the cost effectiveness of tests and procedures that generate incidental findings, including using bundled tests or a battery of tests.[15] Seeking cost effectiveness—an outcome that takes into account both the costs and health outcomes of alternative intervention strategies[16]—in laboratory tests or diagnostic procedures is laudable, and in many cases also might help address the issue of ever-rising health care costs. While there have been some cost-effectiveness studies regarding incidental findings, they have generally been limited in scope.

Recommendation 8

Federal agencies and other interested parties should study the comparative benefits to patients and the cost effectiveness of using bundled tests or a battery of tests versus conducting sequential, discrete diagnostic tests.

To inform individual clinicians, as well as support strong clinical practice guidelines, researchers should conduct reliable comparative- and cost-effectiveness analyses. Evidence regarding comparative benefits to patients of tests that yield

incidental and secondary findings and the cost effectiveness of performing such tests can inform laboratory and payer practices and policies regarding efficient bundling of tests, and can aid clinicians in deciding whether to order a battery of tests rather than sequential, discrete tests.[17]

Clinical Judgment in Managing Incidental Findings

While empirical analysis is critical to informing cost-effective care choices, it is the art of medical decision making that translates data, education, professional guidance, and personal experience into good clinical care. Prudent judgment, understood through Aristotle's concept of *phronesis* (or practical wisdom), constitutes a "capstone" virtue, linking intellectual virtues—such as those that make for good scientists—with the moral character traits such as compassion, trustworthiness, and a sense of justice that make one a particularly good caregiver.[18] Exercising professional judgment is a deliberative process combining formal or "book" knowledge of a professional domain with contextual understanding gained through experience.[19] Although professional judgment is required for every decision that involves considering competing values, principles, or virtues, there is no specific formula by which clinicians identify the right action.[20] Many of the attributes that constitute respected clinical judgment can be cultivated and enabled through classroom and clinical education.

Recommendation 9

Medical educators, both in the classroom and clinic, should continue to cultivate "diagnostic elegance" and "therapeutic parsimony" amongst practitioners—ordering and conducting only tests and interventions necessary for addressing health concerns related to their patient.

Clinicians can minimize the likelihood of incidental findings by engaging in selective diagnostic testing. They can do this by emphasizing thorough communication with patients to better understand symptoms and help narrow the list of potential diagnoses before ordering diagnostic tests. In this way, clinicians can use diagnostic tests to confirm or eliminate specific possible causes of symptoms.

Another important tool that clinicians have to enhance their exercise of professional judgment is the ability to rely on evidence-based standards,

including recommendations from professional organizations. One critical area in which professional organizations make recommendations is preventive screening programs—programs in otherwise healthy populations that aim to identify undiagnosed diseases and conditions before symptoms develop.[21] This type of evidence-based deliberation is critical to ensuring that patients have access to preventive screening programs that offer health care benefits appropriately calibrated to any foreseeable risks—including those that can arise from incidental findings.

Recommendation 10

Professional and public health organizations should produce evidence-based standards for proposed screening programs that take into account the likelihood that incidental findings will arise. Professional organizations should provide guidance to clinicians on how to manage these incidental findings.

The implementation of evidence-based standards in screening programs would assist physicians in exercising clinical judgment about any findings that might arise. Proposed screening programs that take into account the possibility of incidental findings enable clinicians to exercise their professional judgment in deciding whether to conduct a screening test or procedure for a particular patient.

Research Recommendations

Existing scholarship regarding incidental and secondary findings in research reflects both the research community's deep concern for research participants' wellbeing, and an emerging consensus regarding what is ethically required, permissible, and impermissible. The Bioethics Commission therefore makes the following recommendations to guide the ethical management of incidental and secondary findings in the research context.

Consent in the Research Context

In response to the trust imparted to them, researchers owe society and research participants obligations to design and implement research in a responsible manner.[22] During the informed consent process, researchers should describe the types of incidental and secondary findings that might arise to ensure that participants are as informed as possible. This includes, but is not limited to, disclosing anticipatable incidental findings, any

deliberately sought secondary findings, and the possibility of unanticipatable incidental findings.

Researchers should also clearly communicate to participants the plan for disclosing and managing anticipatable incidental findings as well as any possible secondary findings, and the distinction between research and clinical care. This communication is essential to ensure that participants understand what to expect as a result of their decision to participate in research. Clarity with respect to whether and how researchers will disclose anticipatable and unanticipatable incidental findings, and any secondary findings that are deliberately sought, can help sustain public and participant trust in the research enterprise.

Recommendation 11

During the informed consent process, researchers should convey to participants the scope of potential incidental or secondary findings, whether such findings will be disclosed, the process for disclosing these findings, and whether and how participants might opt out of receiving certain types of findings.

If researchers plan to inform participants of certain types of incidental findings, they should decide in advance how to respect the wishes of those who choose to opt out of receiving incidental findings. If researchers have ethical objections to allowing participants to opt out of receiving clinically significant, actionable, and lifesaving findings, they need not enroll such individuals in their research study. Delineating such exclusion criteria for study enrollment will minimize this type of ethically challenging situation once the research protocol is underway.

Alternatively, given that participants have the right to opt out of research at any time,[23] if researchers do not object to allowing participants to opt out of receiving incidental findings—and participants are well informed regarding what opting out could mean for their health and wellbeing—researchers may enroll such participants in the research. In the event a researcher discovers a potentially lifesaving unanticipatable incidental finding for a participant who has opted out of receiving incidental findings, the investigator should seek advice from an institutional review board (IRB) about whether and how to disclose it.

Planning for Incidental Findings in Research

Given that certain findings are predictably associated with a particular modality or type of research, researchers have a duty to anticipate such incidental findings—whether common or rare—to the extent possible. Researchers should develop a plan to manage *anticipatable* incidental findings based on a careful balancing of the risks and benefits of disclosure, along with evidence about the analytic and clinical validity of the findings and their clinical or reproductive significance, in addition to considering actively seeking them as secondary findings. Researchers should submit their proposed plan for the ethical management of incidental findings to an IRB for review and approval. IRBs then would be responsible for assessing the ethical adequacy of the plan.

Recommendation 12

Researchers should develop a plan to manage anticipatable incidental findings, including but not limited to those findings known to be significant and clinically actionable (and, when relevant, analytically valid and clinically valid). The plan should be reviewed and approved by an institutional review board.

Even with an IRB-approved plan for managing anticipatable incidental findings, researchers nevertheless might discover *unanticipatable* incidental findings. The unexpected nature of these findings makes it difficult to ascertain at the outset what responses might be required. Despite, and indeed because of, this uncertainty, researchers should have a process in place ahead of time to manage these unanticipatable incidental findings as well.

When researchers are uncertain whether an unanticipatable incidental finding might have clinical or reproductive significance, researchers should seek out qualified clinical or diagnostic experts for consultation. Consultation with subject matter experts can help researchers resolve uncertainty, determine the significance of the finding, and develop and implement an informed and appropriate response.

Recommendation 13

Researchers should develop a process for evaluating and managing unanticipatable findings. The plan should be reviewed and approved

by an institutional review board. During the informed consent process, researchers should notify participants about the possibility of unanticipatable incidental findings, including lifesaving incidental findings, and the plan for their management. Researchers who discover an unanticipatable incidental finding of concern should assess its significance, consulting with experts as appropriate.

An incidental findings management plan should include specific information regarding the method of disclosure. Nonclinical researchers also might involve clinicians in discussions with participants about incidental findings.

The plan for managing incidental findings should also include a description of the research team's responsibilities following disclosure of such a finding. In some cases, researchers might provide basic educational information about the nature of the finding, advice regarding how to seek care from a clinician or specialist, or guidance about obtaining health insurance to secure treatment. If a clinical specialist is required, researchers should provide the participant with a referral when possible. Disclosure of an incidental finding, however, does not transform a research relationship into a clinical one.

No Duty to Look for Secondary Findings in Research

Researchers' obligations of beneficence raise questions about whether and to what extent they might have a duty to look for secondary findings. While some researchers have research funding to look for secondary findings, this will not be true for many of those conducting valuable research endeavors. Prioritizing a duty to look for secondary findings over the creation of generalizable knowledge has the potential to undermine the research enterprise.

Recommendation 14

Researchers should consider carefully the decision to actively look for secondary findings. In certain circumstances, with approval from an institutional review board, researchers can justifiably adopt a plan that includes looking for selected clinically significant and actionable secondary findings. Approved plans should be disclosed to prospective participants during the informed consent process.

Even without an ethical duty to actively look for secondary findings, researchers could, in some circumstances, justifiably adopt a plan to look for secondary findings. For example, a research team investigating the genetics of a particular community could decide—but would not be obligated—to implement the advice of a community advisory board that recommends looking for a particular variant if requested by a participant, even if the variant is outside the aims of the research. By acknowledging the community's interest and simultaneously completing their research, researchers could advance both the public and individual components of beneficence. Also, while researchers do not have an affirmative duty to look for secondary findings, this does not dilute the importance of developing a plan for managing those that they find and of educating participants about the details of this plan.

Direct-to-Consumer Recommendations

Members of the general public have increasingly gained access to medical tests and procedures outside of traditional clinical or research settings. Situated at the intersection of medicine and business, DTC companies offer the public additional mechanisms for obtaining health-related information. Thus far, the full breadth of DTC activities and their associated ethical considerations have been relatively underexplored in the literature.

Consent in the Direct-to-Consumer Context

DTC testing can offer individuals a means through which they can exercise self determination, including by providing increased access, reduced cost, or greater confidentiality of health information. But the benefits of DTC services are contingent upon the quality of the testing and analyses, and the informed and voluntary nature of the transaction. To enable consumers to make responsible and informed choices regarding DTC testing, consumers must be told what these procedures entail, including the possibility of incidental and secondary findings. Information provided before selecting a DTC procedure can assist consumers in deciding what services are worth pursuing.

Recommendation 15

Direct-to-consumer companies should provide consumers with sufficient information about their services to enable consumers to make informed decisions regarding purchasing their product. Companies should clearly

communicate the scope of procedures and the types of findings that the companies could or will discover and disclose, as well as any findings that they know in advance will not be disclosed.

DTC companies must inform consumers considering their services about the procedures and results included in the commercial arrangement. Among the information needed by consumers is an understanding of the anticipatable incidental findings commonly associated with particular modalities and any secondary findings that will be deliberately sought. If certain results are not returned according to company policy or contractual agreement, this must be disclosed to consumers as well.

Government Regulation in the Direct-to-Consumer Context

From air bags and seatbelts to the proper construction of cribs, the government has responsibility for ensuring the safety of certain products and services offered to consumers.[24] As a matter of policy, society has chosen to impose oversight to place legitimate limits on the principle of *caveat emptor* or "buyer beware."[25] The primary goal of this oversight is to establish consumer protections—to ensure that companies make good on both explicit and implicit guarantees that the goods and services proffered are suitable for the purposes for which companies sell them.[26] Federal and state governments can also provide citizens with assurance that DTC companies are conducting business in a transparent and responsible manner.

Recommendation 16

Federal agencies should continue to evaluate regulatory oversight of direct-to-consumer health services to ensure safety and reliability. State governments should also adopt regulations that ensure a consistent floor of protections for consumers who purchase direct-to-consumer testing.

Policy makers at the state and federal level should examine existing regulations governing DTC services to identify gaps in and barriers to ensuring the safety and reliability of DTC testing. Policy makers should consider adopting regulations governing disclosure of incidental and secondary findings. Policy makers at the state and federal level should remain mindful of the principle of regulatory parsimony, limiting restrictions on the ability to freely engage in commercial transactions only to the extent necessary to prevent serious harm.

Industry-Wide Best Practices in the Direct-to-Consumer Context

The DTC market is relatively new and growing, and the technologies used are often still evolving. Given the diversity in the DTC industry, and the evolving practices employed by DTC companies, DTC companies are uniquely positioned to understand the nature of their own industry. This knowledge could enable DTC companies to develop best practices that are consistent with relevant ethical principles.[27] For example, DTC providers who discover clinically actionable incidental or secondary findings that have health implications could provide consumers with educational information about the nature of the finding, advice about how best to seek care from a clinician or specialist, or even a referral to a clinician who could assist in the management of the finding. If companies adopt voluntary best practices, such best practices could become standard expectations for consumers who choose to undergo DTC testing, giving other companies incentive to adopt and implement these practices, thereby leveling the playing field.

Recommendation 17

Direct-to-consumer companies should aid in the creation of industry-wide best practices concerning the management of incidental and secondary findings. These best practices should include when and how such findings will be disclosed and standards for referral to necessary clinical services. Direct-to-consumer companies should make these "best practices" publicly available to encourage broader adoption.

Voluntary industry-wide best practices can be developed by collaboration among companies and through professional organizations whose members work in the DTC industry. DTC companies should develop best practices regarding disclosure of incidental findings and when secondary findings should be deliberately sought, including the types of findings that ought to be disclosed and the methods for communicating these findings.

CONCLUSION

Although the issue of incidental and secondary findings has been considered by several groups focused on concerns that are context- and modality-specific, the ethical obligations associated with the discovery, disclosure, and management of such findings have not been comprehensively considered across contexts and modalities. This report seeks to fill this void. In *Anticipate and Communicate*, the Bioethics Commission concludes that in any setting, potential recipients should be properly informed about the possibility of incidental or secondary findings before the start of a test or procedure. Practitioners should also recognize the potentially life-changing nature of certain incidental or secondary findings, and should take care to minimize harm when disclosing these findings. Practitioners and potential recipients benefit from empirical evidence about the likelihood of incidental and secondary findings arising from a particular test or procedure. And everyone—practitioners and recipients alike—can benefit from broader, more inclusive discussions about the ethical concerns, and associated practical and legal considerations, raised by incidental and secondary findings.

CHAPTER 1
Introduction

A healthy young medical student participated in research using functional magnetic resonance imaging to look at brain activity while doing a memory test. During this brain scan the researcher noticed a concerning mass. The student rushed to the hospital for further examination, which was followed by successful treatment of the incidental finding that she credits with saving her life.[28]

Two years later, a different woman collapsed from over-hydration while running a marathon. During an evaluation, her emergency care team discovered a small brain tumor. She opted, in consultation with her physicians, for a watch-and-wait approach, monitoring the tumor for changes before making any treatment decisions. She has been watching anxiously for almost 10 years, even though the tumor might never affect her health.[29]

Incidental findings—traditionally defined as results that arise that are outside the original purpose for which the test or procedure was conducted[30]—can create a range of practical, legal, and ethical challenges for recipients and practitioners. Discovering an incidental finding can be lifesaving, but it also can lead to uncertainty and distress without any corresponding improvement in health or wellbeing. For incidental findings of unknown significance, conducting additional follow-up tests or procedures can be risky and costly.[31] Moreover, there is tremendous variation among potential recipients about whether, when, and how they would choose to have incidental findings disclosed. Information that one recipient regards as an unnecessary cause of anxiety could lead another recipient to feel empowered in making health-related decisions.

In this report, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*, the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) focuses on the distinct ethical issues concerning incidental and secondary findings that arise from various modalities—including large-scale genetic sequencing, testing of biological specimens, and imaging—in contexts that include the clinic, research, and direct-to-consumer (DTC) testing. Because the term "incidental findings" as traditionally used can limit consideration of critical ethical issues, the Bioethics Commission considers

several types of ethically challenging findings, including incidental, secondary, and discovery findings, as described below.

Past Consideration of the Management of Incidental and Secondary Findings

Now is an opportune time for a national-level review of the ethics of incidental and secondary findings. The issue of returning incidental findings to research participants was last considered by a national bioethics commission in 1999, when the National Bioethics Advisory Commission (NBAC) issued its report *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*.[32] The NBAC report considered the return of an individual research participant's results rather than incidental findings specifically, and focused only on the research context. In its report, NBAC noted its "presumption that the disclosure of research results to subjects represents an exceptional circumstance" and recommended that researchers return findings only if certain threshold criteria were met: (1) that the findings are scientifically valid and confirmed, (2) that they have significant implications for the participant's health, and (3) that there is a course of action available to ameliorate or treat the associated illness.[33]

In the 14 years since NBAC's report, professional organizations, advisory commissions, and scholars have drafted a number of guidance documents that address the return of incidental findings to patients and research participants. Recommendations outlined in these documents detail and defend various criteria regarding the disclosure of incidental findings (see Appendix I: *Past National Recommendations Regarding Incidental and Secondary Findings* and Appendix II: *Past International Recommendations Regarding Incidental and Secondary Findings*). In contrast to NBAC's recommendations, which assumed as a default position that results should not be returned unless specific conditions could be met, several of these guidance documents explicitly presume routine return of incidental findings. In fact, there seems to be an emerging consensus in some contexts that practitioners have a duty to return some incidental findings—even if there is little consensus as to precisely which ones.[34]

One approach to managing findings in the clinical context was set forth by the American College of Medical Genetics and Genomics (ACMG) in 2013. ACMG advised that laboratories actively look for and return specified findings

that arise from large-scale genetic sequencing regardless of individual patient preferences.[35] Other approaches similarly advocate the return of incidental findings, although they employ different threshold criteria. One approach, following in the footsteps of NBAC, suggests seeking recipient consent to return findings that meet three criteria: analytic validity (the findings are accurate and precise), clinical validity (the findings are causally associated with pathology), and clinical actionability (individuals or practitioners can make use of or act upon the findings for health, personal, reproductive, or clinical decision making).[36]

The current challenge for public policy and professional ethics is to identify through thoughtful deliberation specific criteria that practitioners can use to determine when it is ethically permissible or obligatory for clinicians, researchers, or DTC companies to disclose and not disclose incidental findings to patients, participants, or consumers. The technical aspects of managing the response to incidental findings—including the circumstances under which practitioners should return particular findings—is best carried out by those with the relevant expertise to make those nuanced determinations. Indeed, many professional organizations, advisory committees, and scholars are already hard at work doing just that.[37] In contrast to developing detailed prescriptions for practice, the Bioethics Commission aims through this report to provide a broad ethical analysis of the principles, virtues, and duties relevant to managing incidental and secondary findings to ground these determinations.

In its previous report, *Privacy and Progress in Whole Genome Sequencing*, the Bioethics Commission addressed incidental findings with regard to large-scale genetic sequencing.[38] *Privacy and Progress* made two recommendations concerning incidental findings that arise from whole genome sequencing. The first was a recommendation that practitioners anticipate and disclose the possibility of incidental findings:[39]

Privacy and Progress *Recommendation 3.3*

Researchers, clinicians, and commercial whole genome sequencing entities must make individuals aware that incidental findings are likely to be discovered in the course of whole genome sequencing. The consent process should convey whether these findings will be communicated, the scope of communicated findings, and to whom the findings will be communicated.[40]

The Bioethics Commission also recognized in *Privacy and Progress* that more data were needed to adequately inform this important issue:

Privacy and Progress *Recommendation 3.4*

Funders of whole genome sequencing research should support studies to evaluate proposed frameworks for offering return of incidental findings and other research results derived from whole genome sequencing. Funders should also support research to investigate the related preferences and expectations of the individuals contributing samples and data to genomic research and undergoing whole genome sequencing in clinical care, research, or commercial contexts.[41]

Because the Bioethics Commission specifically focused on protecting individual privacy while advancing the public good through whole genome sequencing, full consideration of the ethical issues associated with incidental findings was beyond the scope of the *Privacy and Progress* report. A more thorough deliberation about the ethical obligations of clinicians, researchers, and DTC providers, as well as consideration of the incidental findings that arise from various diagnostic modalities, is the goal of this report.

Taxonomy of Incidental Findings

The Bioethics Commission notes the challenges associated with deciding on a precise definition of "incidental findings." Several groups have adopted context- or modality-specific definitions (see Table 1.1, *Past Definitions of Incidental Findings*). For example, a working group funded by the National Human Genome Research Institute of the National Institutes of Health offered a research-specific definition of incidental findings as "a finding concerning an individual *research participant* that has potential health or reproductive importance and is discovered *in the course of conducting research* but is beyond the aims of the *study*."[42] The Bioethics Commission used a modality-specific definition of incidental findings in *Privacy and Progress* to cover "information gleaned from *whole genome sequencing research or clinical practice* that was not its intended or expected object."[43] This report focuses on the ethical considerations of incidental findings more broadly.

Table 1.1: Past Definitions of Incidental Findings

GROUP	DEFINITION	CONTEXT/MODALITY
Wolf, et al.[44]	"[A] finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study."	Research/Genetics
Public Population Project in Genomics[45]	"[U]nforeseen findings concerning a research participant that have potential health or reproductive importance. They are discovered during the course of research but are outside its objectives."	Research/Genetics
American College of Medical Genetics and Genomics (ACMG)[46]	"[T]he results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered."	Clinical/Genetics
Munk, et al.[47]	"[F]indings on CT [computed tomography] that are unrelated to the original purpose of the scan...."	Clinical/Imaging
Yanagi, et al.[48]	"[I]ncidentally discovered asymptomatic tumors at the time of examinations of other disorders or screening...." (In reference to the term "incidentaloma")	Clinical/Imaging
Illes, et al.[49]	"[O]bservations of potential clinical significance unexpectedly discovered in healthy subjects or in patients recruited to brain imaging studies and unrelated to the purpose or variables of the study."	Research/Imaging

To date, the term "incidental findings" has generally implied that findings were unanticipated or unintended; this usage is too narrow for the ethical issues considered in this report. Some findings are so likely to arise that they cannot genuinely be considered unanticipated.[50] For example, misattributed paternity is a relatively common finding resulting from blood typing or genetic testing;[51] it would be disingenuous to call this finding *unanticipated*, even though it might be outside the scope of what was being sought, and falls squarely within the category of findings ordinarily considered incidental.

The Bioethics Commission has adopted a definitional framework, based in part on the presentation of Erik Parens at the Bioethics Commission's Meeting 14, that it hopes will help bring conceptual clarity to the variety of findings that can arise (see Table 1.2, *Bioethics Commission's Classification of Individualized Results of Medical Tests*).[52]

Table 1.2: Bioethics Commission's Classification of Individualized Results of Medical Tests

TYPE OF RESULT DISCOVERED	DESCRIPTION	EXAMPLE
Primary Finding	Practitioner aims to discover A, and result is relevant to A	In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered
Incidental Finding: *Anticipatable*	Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place	Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related[53]
Incidental Finding: *Unanticipatable*	Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place	When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not knowable at the time a previous sample was submitted[54]
Secondary Finding	Practitioner aims to discover A, and also actively seeks D per expert recommendation	ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits[55]
Discovery Finding	Practitioner aims to discover A through Z by employing a test or procedure designed to detect a broad array of results	A "wellness scan," a whole body computed tomography (CT) scan, is intended to discover any abnormal finding throughout the body[56]

Under this paradigm, a *primary finding* refers to a result that is actively sought using a test or procedure designed to find that result. Primary findings derive from tests with a single result, such as a blood sugar concentration test related to diagnosing or monitoring diabetes, or the discrete genetic tests for the *BRCA* mutations associated with an increased risk of breast and ovarian cancer (a primary result of a test that recently gained increased public attention when actress Angelina Jolie wrote about her personal experience in the *New York Times*).[57]

For purposes of this report, the Bioethics Commission also divides the term "incidental finding" into two categories: incidental findings that are "anticipatable" and those that are "unanticipatable." An *anticipatable incidental finding* is a finding that is known to be associated with a test or procedure. Anticipatable incidental findings need not be common or even likely to occur—their defining characteristic is that the possibility of finding them is known. For example, anticipatable incidental findings often arise

when using imaging technologies, such as computed tomography (CT) scans, because a certain organ is the intended focus of the scan but other structures also appear in the field. A CT scan of the colon might show a mass on an adjacent kidney, for example. Because practitioners can anticipate these types of findings at the outset of a test or procedure, anticipatable incidental findings should be planned for to the extent possible. Plans for managing anticipatable incidental findings do not, however, necessarily require that the findings be disclosed; for example, many argue that the anticipatable incidental finding of misattributed paternity often should *not* be disclosed.[58]

The second category of incidental findings is an *unanticipatable incidental finding*. This category includes a finding that could not have been anticipated given the current state of scientific knowledge. For example, a DTC genetic testing company could inform its customers that not all genetic variants are currently associated with particular medical information but that, over time, variants that are not currently associated with disease might later become associated with medical information that had not been foreseen.[59] Although practitioners are not expected to have a plan in place to manage specific findings that they could not anticipate, they nevertheless must respond appropriately to unanticipatable incidental findings that arise.

A *secondary finding* refers to a finding that is actively sought by a practitioner that is not the primary target. Practitioners might actively seek secondary findings when doing so is recommended by an expert body, or by a consensus of practitioners, as ethically and medically appropriate. For example, a clinician who conducts large-scale genetic sequencing for the purpose of diagnosing a patient's disease might nevertheless deliberately seek the additional phenotypic variants (associated with physical characteristics) recommended by ACMG. However, few lists of secondary findings recommended by experts currently exist. As more expert panels determine the findings that practitioners ought to look for when using certain modalities, some findings that were *anticipatable* incidental findings will likely become *secondary* findings that practitioners should specifically seek.

A *discovery finding* refers to the results of a broad or wide-ranging test that was intended to reveal anything of interest. For example, "wellness scans" are whole body scans marketed by hospitals and DTC companies to detect disease in all parts of the body before symptoms exist.[60] The "tell me everything"

aspect of these tests means that practitioners target all findings and none of the results are technically "incidental." Nevertheless, discovery findings often can be sensitive or surprising to the patient, participant, or consumer.

This report focuses on anticipatable and unanticipatable incidental findings as well as secondary findings. For simplicity, the generic term "incidental finding" is used in reference to both anticipatable and unanticipatable incidental findings; distinctions are made as necessary and relevant.

Ethical Basis of the Management of Incidental and Secondary Findings

Longstanding ethical principles ground the Bioethics Commission's consideration of incidental and secondary findings. In seeking to create mutually acceptable and justifiable public policy, a process of democratic deliberation can lead citizens, policy makers, and experts to identify common ground and compromise.[61] Because professionals in a variety of contexts—including clinical, research, and DTC—can encounter incidental and secondary findings, guidance must appeal to principles that bridge these contexts. The interpretation, application, scope, strength, and stringency of each principle, however, can vary among and within each context.

Ethical action is not only a matter of principles, but also involves fulfilling duties owed to others. Such duties can result from promises and commitments made by professionals, from the relationships between practitioners and recipients, and from the contexts in which professionals operate. The interpretation of each principle in the clinical, research, and DTC contexts helps clarify the duties of practitioners with respect to incidental and secondary findings, and how practitioners can fulfill these obligations responsibly.

The ethics of incidental and secondary findings also involve notions of character, or virtue. Virtues are those character traits associated with moral and professional excellence, such as honesty, courage, and humility.[62] The question of what to do about an incidental finding that arises involves striving for excellence in making professional judgments. In its deliberations, the Bioethics Commission found that context-specific interpretation and application of ethical principles calls for attributes such as prudent professional judgment.

The Bioethics Commission found four ethical principles to be particularly applicable to the ethical assessment of incidental and secondary findings: respect for persons, beneficence, justice and fairness, and intellectual freedom and responsibility. A context-specific interpretation of each principle is necessary to translate the principles into actionable guidance, and is undertaken in each of the context-specific chapters.[63]

The principle of *respect for persons*, as articulated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in *The Belmont Report*, recognizes the fundamental human capacity for rational self-determination—the autonomous ability to identify personal preferences, act on these desires, and direct the course of one's life.[64] For the purposes of this report, the principle of respect for persons is interpreted as freedom from limitations that prevent meaningful choice and encompasses dignity and the right to available information even if it does not affect a person's choice.[65]

The principle of *beneficence* calls on professionals to take actions to ensure the wellbeing of others, while its corollary *non-maleficence* requires not imposing harms on others.[66] In all contexts, the driving concern captured by this principle is to take actions that offer a prospect of benefit sufficient to justify any related risks of harm.[67] One specification of the principle of beneficence is the duty to rescue, an obligation to come to the aid of others facing dire peril when such assistance is easy to provide.[68] The related duty to warn is a special case of the duty to rescue, when rescue itself is either impossible or imposes significant costs.[69] These basic ethical obligations exist among all members of society, but special professional obligations of clinicians, researchers, and DTC providers are more stringent than the low-level duties to rescue or warn imposed upon mere strangers. Disclosure of serious incidental and secondary findings in the three contexts examined here can be seen as arising from more complex, and often more robust, professional relationships.

Specifying the principle of beneficence, the Bioethics Commission, in its first report, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, further articulated the principle of *public beneficence*, which supports society in the pursuit of public benefit while minimizing personal and public harm.[70] Public beneficence involves a commitment to improving health care as a whole.

As applied to incidental and secondary findings, public beneficence demands consideration of the needs of key stakeholders—including clinicians and patients, researchers and participants, and DTC providers and consumers—along with the costs and benefits to society more broadly.

The principle of *justice and fairness* requires fair and equitable treatment of all. There are three interpretations of this principle pertinent to managing incidental and secondary findings. First, the principle of justice and fairness calls upon individuals and institutions to make reasonable efforts to ensure that the benefits and burdens of an enterprise are distributed equitably among those who might be affected.[71] Second, a society committed to justice and fairness must assess claims regarding what individuals or groups are entitled to receive—that is, what they can reasonably and legitimately expect of others.[72] Third, justice requires that ethically similar cases be treated alike.

Finally, the principle of *intellectual freedom* protects sustained and dedicated creative intellectual exploration that furthers scientific progress.[73] Along with the freedom of intellectual pursuits, clinicians, researchers, and providers of DTC testing must take *responsibility* for their actions, acknowledging the profound societal trust placed in them, and the trust afforded them by patients, participants, and consumers.[74] The principle of *intellectual freedom and responsibility* can be interpreted as a rejection of the technological imperative: the mere fact that something new can be done does not mean it ought to be done.[75] With regard to incidental and secondary findings, although technology increasingly enables us to discover more, the information gained does not always further individual or collective wellbeing. Incidental and secondary finding policies should be designed, in accordance with the corollary principle of *regulatory parsimony*, to limit oversight to that which is necessary to further the public good.

The Bioethics Commission's Process

In concert with the principle of democratic deliberation, the Bioethics Commission invited experts from the public and private sectors; individuals affiliated with the clinical, research, and DTC contexts; and those with specialties in several modalities to inform and engage with the Bioethics Commission in its discussions. Over the course of four public meetings, speakers addressed the ethical, legal, scientific, and practical issues associated

with incidental and secondary findings (see Appendix III: *Guest Presenters to the Bioethics Commission Regarding Incidental and Secondary Findings*). The Bioethics Commission also published a Request for Information in the *Federal Register* that elicited many thoughtful comments from individuals and professional societies in the United States and from around the world.[76] The contributions were incorporated into the Bioethics Commission's deliberations and this report.

About this Report

Using the above guiding principles, *Anticipate and Communicate* explores the ethical obligations of practitioners to manage incidental and secondary findings. While it focuses on specific modalities and settings as examples, the Bioethics Commission intends the ethical principles, analyses, and recommendations articulated here to guide the ethical management of incidental and secondary findings regardless of how or where the finding arises.

Chapter 2 provides an overview of the incidental and secondary findings that arise from particular modalities, specifically large-scale genetic sequencing, testing of biological specimens, and imaging. Chapter 3 sets forth overarching recommendations that apply across contexts. Chapters 4, 5, and 6 explore context-specific concerns that arise when managing incidental and secondary findings in the clinic, research, and DTC settings. Recognizing that practical and legal realities can limit the scope and stringency of a practitioner's obligations with regard to incidental and secondary findings, each of these chapters begins with an overview of the practical issues unique to each context, addresses some of the pertinent legal concerns, and then applies the governing ethical principles. Each chapter concludes with an analysis of these considerations and provides recommendations for the ethical management of incidental and secondary findings. Although the framework developed with a particular focus on three specific contexts, the Bioethics Commission intended the ethical analysis to be relevant and applicable in other settings. Chapter 7 summarizes the Bioethics Commission's approach.

CHAPTER 2
Modalities and Probable Incidental and Secondary Findings

Many tests and procedures can give rise to incidental and secondary findings. At one end of the spectrum are discrete tests that produce only the particular result sought and are therefore unlikely to give rise to incidental and secondary findings—for example, pregnancy and HIV tests. At the other end of the spectrum are broad diagnostic tests, such as direct-to-consumer (DTC) full body scans, for which the intended purpose is to find any existing abnormality. These tests have such a broad and all-encompassing aim that few of the findings can be considered "incidental."

> "All technological changes and all scientific discoveries that lead to technological changes have unexpected outcomes."
>
> Cowan, R.S., Janice and Julian Bers Professor Emerita, History and Sociology of Science, University of Pennsylvania. (2013). Ethical Challenges of Emerging Technologies. Presentation to the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission), April 30. Retrieved from http://bioethics.gov/node/1616.

Between discrete and broad diagnostic tests are tests and procedures most likely to give rise to incidental and secondary findings. These tests are designed to give practitioners the results sought, but also have the potential to reveal other findings. In some cases, the potential for incidental and secondary findings is inherent in the test. For example, imaging technologies often capture surrounding organs, or areas outside the purpose for which the test was originally conducted. In other cases, because of insurance reimbursement schemes or cost guidelines, practitioners order bundled tests that reveal both the targeted result along with other results outside the scope of the intended purpose.

This chapter describes three categories of analytical techniques likely to give rise to incidental and secondary findings—large-scale genetic sequencing, testing of biological specimens, and imaging—to help elucidate the ethical analyses that follow.

Large-Scale Genetic Sequencing

Genetic sequencing is the analysis and ordering of the billions of base pairs—the As, Ts, Cs, and Gs—that make up our genetic code. Interpretation of this sequence can predict propensities to develop some diseases.[77] Information that could be discovered includes a propensity toward contracting heritable genetic diseases like breast cancer or Huntington's disease (a fatal neurodegenerative disorder for which there is currently no treatment available).[78] Large-scale genetic sequencing—encompassing whole genome sequencing, whole exome sequencing, and other next-generation genomic analyses—is increasingly used

to investigate the genome. As the price of whole genome sequencing continues to fall—from about $95 million in 2001 to $5000 in 2013[79]—clinicians, researchers, and DTC companies increasingly are conducting large-scale genetic sequencing. Despite the falling costs of sequencing, translating and interpreting the genetic sequence is challenging and time-consuming and generally requires the skills of qualified experts.[80]

> "[T]his idea of data sort of popping out at you and being unexpected doesn't really reflect…the way that genomic data have to be analyzed, because [they have] to be interpreted in a way, and you have to decide what things you are going to look for, especially when you have a massive amount of information."
>
> Cho, M., Associate Director and Professor of Pediatrics, Stanford University Center for Biomedical Ethics. (2013). Incidental Findings in Genomics: Ethical Frameworks and Practical Challenges. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1616.

Because of the large number of base pairs analyzed, large-scale genetic sequencing has the potential to yield large numbers of incidental and secondary findings. While some variants discovered during large-scale genetic sequencing reveal clinically relevant information, much is of unknown or uncertain medical value.[81] As the science evolves, variants that are of unknown significance today could later be discovered to be associated with important diseases or conditions.

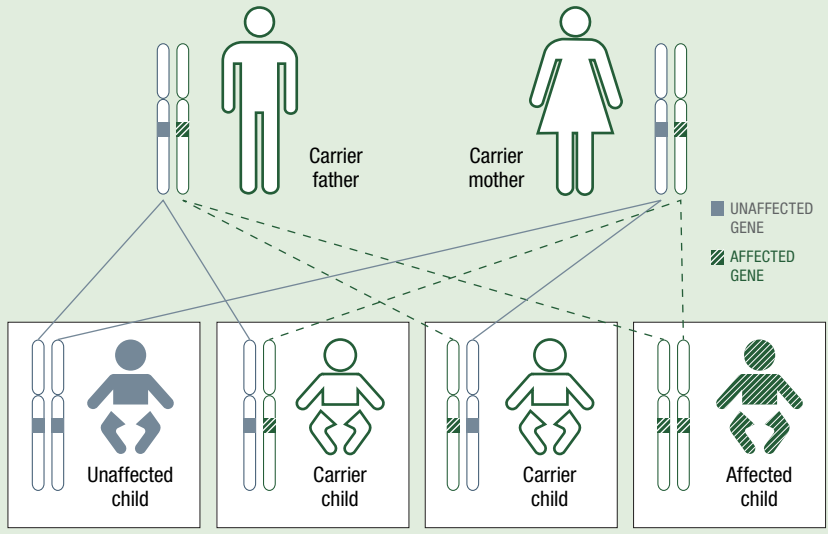
Incidental and secondary findings that arise in genetic sequencing raise an additional concern: genetic information has implications not just for the individual tested, but for biologically-linked family members as well. Genetic information is heritable, and biologic family members share many genetic traits. Individuals should therefore consider the implications of seeking information that could affect third parties.[82] One implication is uncertainty about a practitioner's obligation to alert at-risk family members of particular genetic predispositions, or to recommend that persons tested disclose any predisposition to their at-risk family members.[83] Practitioners could also face barriers to disclosing confidential medical information to family members not otherwise authorized to access this information.[84]

In the clinical context, clinicians increasingly employ large-scale genetic sequencing for "the molecular characterization of rare diseases, the individualization of treatment (particularly in cancer), pharmacogenomics, preconception/prenatal screening and population screening for disease risk."[85] Recent recommendations developed and advanced by the American College of Medical Genetics and Genomics (ACMG) recommended that laboratories seek and report findings

that arise from clinical large-scale genetic sequencing related to 24 phenotypes associated with disease that "have been previously reported and are a recognized cause of the disorder or variants that are previously unreported and are of the type which is expected to cause the disorder."[86]

In the research context, researchers often use large-scale genetic sequencing to ascertain underlying genetic causes of disease. Any findings that arise outside the primary area of inquiry—for example, findings that are not the target of research, but that might nevertheless have reproductive significance for the participant—are incidental or secondary.

CASE STUDY



GENETIC RESEARCH

A woman of childbearing age contributes her genetic material to a research study. Although the researchers' primary interest is in gathering data about genetic factors related to fertility, they employ whole genome sequencing given their interest in a wide array of variants. In the course of analyzing the data, the researchers discover that this individual is a carrier for Tay-Sachs disease, a genetic condition resulting from mutations in the *HEXA* gene on chromosome 15. When an individual inherits two copies of the mutation, Tay-Sachs disease manifests as nerve damage and early death. If this individual were to conceive with another carrier, there is a 25 percent chance in each pregnancy that the child would develop the disease.

Sources: National Library of Medicine. (2012). Tay-Sachs disease [Webpage]. Retrieved from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002390; National Institutes of Health (NIH). (2008). Genetics Home Reference: HEXA. Retrieved from http://ghr.nlm.nih.gov/gene/HEXA.

Several DTC companies provide large-scale genetic sequencing directly to consumers to determine genetic susceptibility or carrier status for a wide range of diseases and traits.[87] 23andMe currently returns findings for over 240 diseases and traits.[88] These findings, though perhaps surprising to the customers receiving them, are "discovery findings" rather than incidental because they are within the scope of findings sought. Still, despite the broad nature of the testing, some findings *can* be incidental. For example, genetic sequencing can reveal an unknown or unrecognized discrepancy between chromosomal sex and reported sex, a mismatch between an individual's chromosomal and biological sex—an anticipatable incidental finding that is not listed as one of the conditions to be returned or disclosed in the company's terms of service.[89] DTC genetic testing also might give rise to unanticipatable incidental findings if genetic associations to specific diseases are discovered after the initial testing of a consumer's sample. 23andMe, for example, continually reexamines consumers' genetic sequences as new tests become available, and sends consumers an email notifying them that additional results are available.[90]

> "Basically, anything we can tell you on the basis of your DNA is part of the package, but things might at some point get beyond what we might have expected. And there's a difference between what is spelled out as a broad set of information you might receive and what you might have expected."
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> Mountain, J., Senior Director of Research, 23andMe. (2013). Incidental Findings: A 23andMe Perspective. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1620.

Testing of Biological Specimens

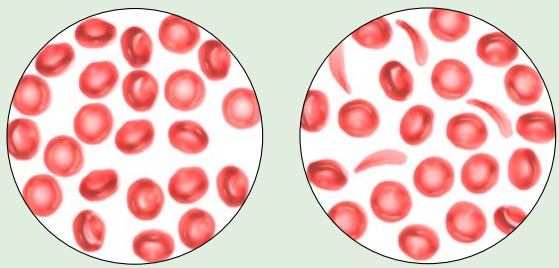
Biological specimens such as blood, urine, or other tissues can also be the source of incidental or secondary findings. Incidental and secondary findings arising from blood and tissue testing could definitively indicate a health issue of concern, or could require a series of additional diagnostic tests to determine the health implications, if any, of the result.

Diagnostic tests on biological specimens can give rise to incidental and secondary findings in the clinical context. Although clinicians are generally trained to order tests targeted to inform clinical management, clinicians nevertheless might order a battery of tests—multiple tests ordered simultaneously to ascertain the cause of a problem—to increase efficiency or might order bundled tests if dictated by laboratory practice or insurance reimbursement.[91] For example, a practitioner might order a comprehensive

metabolic panel (a panel of 14 blood tests providing a general assessment of kidney and liver function and electrolyte and fluid balance) to assess kidney function, but the laboratory results might reveal an incidental finding of liver dysfunction.[92] Ordering a larger number of tests increases the likelihood of obtaining an abnormal test result, which could lead to additional tests or follow-up procedures that can expose patients to additional risk.[93]

In the research setting, incidental and secondary findings might arise when testing biological specimens for study purposes or while ascertaining a prospective participant's eligibility to enroll in a study. A researcher could discover that a participant has elevated blood sugar, possibly indicating diabetes, or notice irregularly shaped red blood cells that could indicate sickle cell carrier status.

CASE STUDY



Unaffected blood sample

Blood sample of a carrier of one copy of sickle cell gene (asymptomatic)

INCIDENTAL FINDING OF SICKLE CELL TRAIT

One example of an incidental finding in research with biological specimens is the discovery of cells exhibiting a sickle shape in a blood sample being examined for other purposes (depicted in the picture above). Unlike individuals with two copies of the gene, carriers of one copy of the sickle gene can have blood cells that exhibit the sickle shape without having symptoms of disease. But due to the unique shape of the blood cells, the individual's carrier status is ascertainable by laboratory technicians. The finding could have personal utility (e.g., an individual could choose to hydrate well before climbing to high altitudes or exercising vigorously) and reproductive significance (e.g., offspring could inherit the variant) for the participant.

Source: U.S. Centers for Disease Control and Prevention (CDC). (n.d.). What You Should Know About Sickle Cell Trait. Retrieved from http://www.cdc.gov/ncbddd/sicklecell/documents/SCD%20factsheet_Sickle%20Cell%20Trait.pdf.

A number of companies offer DTC testing of biological specimens including testing of blood, fecal matter, and urine.[94] Generally, consumers order targeted, discrete tests or comprehensive panels that list included tests. Incidental or secondary findings might arise if, despite the consumer's primary interest in a particular result, the consumer orders a comprehensive panel rather than an individual test because it is more cost effective.[95]

Imaging

Medical imaging—a modality that includes magnetic resonance imaging (MRI), computed tomography (CT) scans, X-rays, neuroimaging, and ultrasounds, along with techniques such as electroencephalography and electrocardiography that give rise to data capable of being represented as images—can lead to incidental and secondary findings. Imaging products report results of the entire field of view, even if outside of the area of diagnostic interest. For example, MRI and CT scans of the abdomen and pelvis can include images of the kidneys, liver, adrenal glands, and pancreas—with the associated possibility of discovering incidental and secondary findings in any of those organs. The likelihood of encountering incidental findings using imaging techniques is high, even among asymptomatic individuals, but few of these findings have serious or any health consequences.

Imaging methods are used, and incidental and secondary findings arise, in the clinical, research, and DTC contexts. In the clinic, imaging technologies often reveal findings that are outside the scope of the diagnostic purpose of the test. One of the more widely used clinical imaging techniques is CT, which processes X-ray images from multiple angles to create tomographic images of the body.[96] Of particular concern are abdominal CT scans in which incidental findings are identified in an estimated 30 to 35 percent of scans.[97] In a study of CT scans of patients at a trauma center, 43 percent of patients had at least one incidental

> "Further compounding the lack of awareness of the likelihood of incidental findings on imaging is the lack of standardized reporting of such findings in the radiology report…the same type of incidental finding may be reported five different ways by five different radiologists influenced by years in practice, comfort with the modality in interpretation, fear of malpractice, and even knowledge of the referring physician's practice patterns or known patient risk factors."
>
> Berland, L.L., Chair, American College of Radiology. (2013, July 5). Comments submitted to the Bioethics Commission.

finding.[98] Incidental findings are so common in abdominal CT scans that, even among patients who present with trauma, physicians are more likely to discover incidental findings than any evidence of traumatic injury.[99] Factors such as the field of view captured by the image, the diagnostic purpose for which the test was ordered, and the expertise or specialty of the practitioner tasked with interpreting the image, can influence the frequency of incidental and secondary findings that arise in the clinical context.

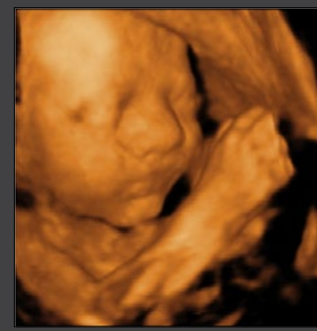
> "[T]he harder you look, the more you will find. It's a continuum.... With our research grade scans, we won't really find much.... If you do clinical grade scans, you will more likely find... more. Where do you draw that line in terms of how much effort you put into the quality of your research scans?"
>
> Bandettini, P., Chief, Section on Functional Imaging Methods, Laboratory of Brain and Cognition, National Institute of Mental Health. (2013). Issues Regarding the Management of Incidental Findings in Neuroimaging. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1617.

Scan-related incidental and secondary findings also arise in research. Research-grade scans are often of lower clinical utility than clinical-grade scans. They are often less expensive and designed to hone in on a particular finding. Because they are performed to answer a research question rather than address a participant's medical need, they are generally less useful than traditional clinical scans for diagnosing or characterizing an unknown mass.[100] This difference in clinical utility has implications for both the detection and interpretation of incidental and secondary findings in the research context. For example, to assuage concerns that research scans do not provide clinical resolution, the intramural research program of the National Institutes of Health requires annual clinical-grade scans of all brain imaging research participants.[101]

In DTC settings, full body, partial body, and targeted organ CT and MRI scans are available without a medical practitioner's order.[102] These tests are generally marketed as preventive—offering early disease detection.[103] DTC companies generally market full-body CT scans or whole body MRI for the purpose of identifying *all* abnormalities. Certain types of DTC imaging could, however, give rise to incidental findings. For example, CT scans of the colon for polyps often identify problems with organs other than the colon.[104] A number of DTC companies also offer non-medical fetal ultrasounds, marketed as providing 2-, 3-, and 4-dimensional ultrasound pictures and videos of the fetus (see Figure

2.1, *An Example of a 3-D Fetal Ultrasound Taken by a Direct-to-Consumer Company*).[105] Although companies generally state that they do not intend their ultrasounds to provide medical information,[106] an "entertainment-only" ultrasound can reveal fetal anomalies.[107] Some companies explain how they will communicate any abnormal findings, but typically there are no physicians on site to initiate counseling and the level of expertise among the technicians performing DTC fetal ultrasounds varies.[108] Moreover, the clinical significance of variations might be ambiguous, particularly with newer, higher powered ultrasound technology that can display images of previously unidentifiable structures.[109]

Figure 2.1: An Example of a 3-D Fetal Ultrasound Taken by a Direct-to-Consumer Company



Conclusion

The increasing technological capability of the modalities discussed in this chapter leads to an increased likelihood of discovering incidental and secondary findings. The movement from discrete genetic tests toward large-scale genetic sequencing increases the likelihood that clinicians, researchers, and DTC providers will confront the issue of incidental and secondary findings. Likewise, imaging technologies are increasingly able to detect anomalies that were previously undetectable, making incidental findings more likely to be discovered. And as payment structures evolve so that bundled tests are presumed to be more cost effective than discrete tests, the number of unintended findings is expected to increase. The Bioethics Commission recognizes that a variety of tests and procedures, including but not limited to those discussed above, give rise to incidental and secondary findings and therefore intends the ethical analysis and recommendations in this report to apply widely to the management of all incidental and secondary findings.

CHAPTER 3
Overarching Recommendations for Incidental and Secondary Findings

Although many ethical considerations concerning the management of incidental and secondary findings are specific to the setting in which they occur—and the type of relationship between the practitioner and the potential recipient—there are several important considerations applicable to such findings in *all* contexts. This chapter articulates these unifying recommendations that span all contexts. These recommendations include the importance of informing individuals about incidental and secondary findings; the need for evidence-based practice guidelines, additional empirical research, and stakeholder education; and the requirements of justice and fairness in access to counseling and health care.

Informing Persons Tested

In all contexts, potential recipients of incidental and secondary findings—patients, research participants, and consumers—should be informed about the likelihood of such findings arising from a particular test or procedure. Providing this information enables a potential recipient to make an autonomous decision about whether and how to proceed. This disclosure also allows practitioners to anticipate and think through the consequences of conducting various tests and procedures. Open communication between practitioners and individuals, accessible and understandable documents and resources, and transparent processes in all three contexts help ensure that individuals understand risks and benefits before they consent.

In each context, the informed consent process should be facilitated, rather than discouraged or disincentivized. Better informed consent in the clinic decreases the likelihood of confusion or miscommunication about follow-up and treatment decisions. More transparent and understandable informed consent in the research setting facilitates trust in the research enterprise. And more accessible and understandable information provided to direct-to-consumer (DTC) consumers can help decrease anxiety and confusion about results.

Recommendation 1

Clinicians, researchers, and direct-to-consumer providers should describe to potential recipients incidental and secondary findings that are likely to arise or be sought from the tests and procedures conducted. Practitioners should inform potential recipients about their plan for disclosing and managing

incidental and secondary findings, including what findings will and will not be returned.

Practitioners should facilitate and work to improve the process of informed consent in all contexts. Adequately informing individuals about the potential for discovering incidental findings should include an explanation of the nature of anticipatable incidental findings, as well as the possibility of discovering unanticipatable incidental findings, and a thorough description of any secondary findings that will be sought.

Informing individuals about the nature of incidental and secondary findings likely to arise, and the practitioner's plan for their management and disclosure, is critical in all contexts, but should be implemented differently in each. For further context-specific analysis and application, see Recommendation 6 in Chapter 4 for implementation in the clinical context, Recommendation 11 in Chapter 5 for implementation in the research context, and Recommendation 15 in Chapter 6 for implementation in the DTC context.

Evidence-Based Practice Guidelines

Practice guidelines can inform practitioners about the anticipatable incidental findings likely to arise during common tests and procedures, and the ways in which practitioners can best manage these findings—including the possibility of actively seeking particular findings as secondary findings. Guidelines tailored to each modality, procedure, or test that address the findings that arise in each context can help practitioners develop their own ethically sound policies for managing such findings.

A number of professional societies and institutions—including the American College of Medical Genetics and Genomics, the American Medical Association, the American Cancer Society, the American College of Preventive Medicine, and the U.S. Preventive Services Task Force—have promulgated recommendations and guidelines that seek to provide best practices for various medical tests and procedures.[110] One such example is the American College of Radiology Incidental Findings Committee's guidelines on the management of incidental findings in abdominal computed tomography (CT) scans. These guidelines establish and recommend management systems based on the characteristics of the incidental finding in question.[111] In the clinical context, the Endocrine Society developed guidelines that delineate

what clinical action should be taken for incidental findings discovered on the pituitary gland, including whether and when to conduct follow-up testing, and what further diagnostic steps to take.[112]

> "I think we need…to recognize a population-focused and evidence-based reasoning for using diagnostic tests—for pursuing odd findings and so forth."
>
> Morreim, H., Professor, Department of Internal Medicine, College of Medicine, University of Tennessee Health Science Center. (2013). Incidental Findings in the Clinic. Presentation to the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission), April 30. Retrieved from http://bioethics.gov/node/1619.

Groups have also proposed approaches for categorizing incidental findings that arise in research into those that should, might, or should not be disclosed. For example, a working group of the National Heart Lung and Blood Institute provided examples of genetic variants discovered during research that they believe should not be withheld absent an expressed participant preference for non-disclosure; these determinations were made on the basis of clinical actionability and gene penetrance (the degree to which the disease risk is elevated by a genetic mutation).[113]

Across contexts, evidence-based practice guidelines can bolster a practitioner's ability to make decisions about how best to manage incidental and secondary findings. Guidelines developed within medical specialties should elucidate the types of incidental findings that might arise in common tests and procedures, findings that should be actively sought as secondary, salient features that might indicate a serious problem warranting immediate follow up, factors that indicate cause for potential concern that should be observed, and relevant features that might denote a lack of medical significance. Based upon these parameters, specialty-specific guidelines can recommend reasonable courses of action in each scenario.

Recommendation 2

Professional representative groups should develop guidelines that categorize the findings likely to arise from each diagnostic modality; develop best practices for managing incidental and secondary findings; and share these guidelines among practitioners in the clinical, research, and direct-to-consumer contexts.

Professional and institutional guidelines are crucial to ensuring consistent and systematic categorization, disclosure, and management of incidental and

secondary findings. Professional societies and institutions should continue to identify anticipatable incidental findings and develop evidence-based best practices for managing them.

In developing guidelines, professional organizations should employ a variety of criteria, including clinical significance and actionability. Personal utility might be another factor included in any assessment as it allows a recipient to make different life choices (such as improving nutritional habits or keeping apprised of new medical developments), change life priorities, plan for the end of life, or simply develop a better understanding of themselves.[114] Practice guidelines also should take into account the economic costs associated with conducting additional diagnostic tests in relation to ascertainable benefits. Different findings could have vastly different economic impacts depending on the nature and amount of follow-up required.

As professional organizations increasingly recognize certain anticipatable findings likely to arise from particular tests and procedures, and determine that certain findings are sufficiently significant and actionable to merit disclosure, a number of findings—previously considered anticipatable incidental findings—are likely to become actively sought secondary findings. The transition from unanticipated incidental findings to anticipated or secondary findings allows more information to be provided to potential recipients and therefore facilitates more meaningful consent across contexts.

Additional Empirical Research

Additional empirical research and scholarship is needed concerning the discovery, disclosure, and management of incidental and secondary findings. In its report, *Privacy and Progress in Whole Genome Sequencing*, the Bioethics Commission recommended that funders of whole genome sequencing research conduct further studies to evaluate proposed frameworks for offering to return incidental findings and other research results.[115] The Bioethics Commission continues to believe that additional empirical data are critical to informing the ethical management of incidental and secondary findings, and therefore suggests expanding the scope of such recommended empirical research.

Research regarding the incidental and secondary findings that arise from a variety of modalities can help establish rigorous, evidence-based best practices

that can guide practitioners across contexts. To date, the limited empirical research regarding incidental and secondary findings has primarily focused on findings that arise in the clinical and research contexts.[116] Scholarship focusing on incidental findings in the DTC context is even more limited. There are also limited empirical data on the preferences of potential recipients concerning disclosure and management of incidental findings.[117]

Recommendation 3

Federal agencies and other interested parties should continue to fund research regarding incidental and secondary findings. This research should consider the types and frequency of findings that can arise from various modalities; the potential costs, benefits, and harms of identifying, disclosing, and managing these findings; and recipient and practitioner preferences about the discovery, disclosure, and management of incidental and secondary findings.

Data about incidental and secondary findings can come from a variety of sources. One potential source is practitioners gathering information about incidental and secondary findings through their work, monitoring findings that arise, and developing databases about the disclosure and management of such findings.[118] Professional societies also can address specific questions about findings likely to arise from various modalities and in various contexts and the professional skills or training necessary to interpret and manage these findings.[119]

Research groups funded by the National Institutes of Health—including those led by Susan Wolf, Judy Illes, and Robert Green—have focused on the management of incidental findings that arise in the research and clinical contexts.[120] The National Institutes of Health, the U.S. Centers for Disease Control and Prevention, and other public and private entities should continue to conduct research to inform the development of evidence-based and ethical policies for the management of incidental and secondary findings. Moreover, given that the technologies that give rise to incidental and secondary findings are fast-moving and ever evolving, the research questions that accompany these technologies will continue to evolve. Research questions should therefore seek to keep pace with advances in technology.

Educating Stakeholders

Educating the public about incidental and secondary findings enables those undergoing tests or procedures to make better informed decisions and develop informed preferences about receiving potential findings. Educating practitioners about their ethical obligations enables them to make more thoughtful decisions about how to anticipate, disclose, and manage incidental and secondary findings.

For example, the National Cancer Institute's "Pink Book" offers practical tools to better understand target audiences, develop materials with appropriate attention to health literacy, and identify and implement strategies through various communication channels including mass, digital, and social media.[121]

EXAMPLE IN ACTION

THE NATIONAL CANCER INSTITUTE'S PINK BOOK

The National Cancer Institute has published a "Pink Book," a guide for health care providers designed to facilitate and improve health care communication. The detailed document is geared toward public health officials in a diverse array of settings. It outlines techniques for communicating with the public to improve health that are supported by research, case studies, and complex behavioral psychology. The Pink Book details specific methods for communication and guides public health officials in making choices regarding messaging, cultural sensitivity, media choice, program testing, implementation, and assessment. Some of the programs described include efforts to increase the number of women in a community who get annual mammogram screenings, public education about high blood pressure, and prescription drug abuse prevention.

Source: National Cancer Institute. (n.d.). Pink Book - Making Health Communications Work. Retrieved from http://www.cancer.gov/cancertopics/cancerlibrary/pinkbook/page1.

Federal, state, and local public health institutions and patient and health professional organizations should also play a role in educating the public.[122] Employing proven, evidence-based methods of health communication is critical to help individuals make informed choices about the possible benefits and harms of testing in light of the possibility of incidental and secondary findings. Effective communication also might increase the likelihood that specific findings—for example, the presence of a genetic marker (or a lack thereof) for cardiovascular disease—will contribute to positive health behaviors.[123]

Recommendation 4

Public and private entities should prepare educational materials to inform all stakeholders—including practitioners, institutional review boards, and potential recipients—about the ethical, practical, and legal considerations raised by incidental and secondary findings.

In addition to the educational efforts of the Bioethics Commission, a wide variety of groups, governmental bodies, and professional organizations can assist in educating stakeholders about incidental and secondary findings. For example, private institutions such as the American Association of Medical Colleges and the Accreditation Council for Graduate Medical Education can provide guidance to clinicians about managing incidental and secondary findings.

Public and private entities tasked with providing education about and regulation of medical research can bolster existing materials to better address the ethical issues raised by incidental and secondary findings. For example, Public Responsibility in Medicine and Research (PRIM&R) has an IRB education and IRB professional certification program that could provide training to IRB members on these ethically challenging topics.[124] Governmental bodies, like the U.S. Federal Trade Commission and the Food and Drug Administration, can provide guidance on their websites to educate the public about the types of findings that DTC technologies can discover. Although such education is not the traditional role of these government agencies, when agencies make decisions that affect the public and other stakeholders, they should issue statements explaining their policies to foster public trust and understanding.

Policies for educating stakeholders about the complex ethical considerations and practical realities of incidental and secondary findings should draw from multidisciplinary research about health communication and decision making.[125] Because incidental findings are often characterized by uncertainty and can require conveying complex information, certain guiding principles should be employed. These include enhancing trust through transparency and stakeholder engagement, and incorporating emotional, social, cultural, and other experiential factors into communication methods.[126] Educating

clinicians, researchers, and providers of DTC testing about the ethical, practical, and legal concerns associated with incidental and secondary findings is critical to fostering a culture of professional responsibility.

Justice and Fairness and Health Inequities

Justice and fairness in health care requires that all individuals have access to adequate affordable services to meet basic health care needs. Our society should continue to seek cost-effective ways to provide affordable access to health care to as many individuals as possible. The right test at the right time can be lifesaving, while over-testing comes with its own risks that can be detrimental to both mental and physical health. Adequate, affordable care provides the backdrop against which competent health care professionals can offer expert advice, personalized counseling, and follow-up care to harness the benefits of these developing diagnostic technologies. Coupling counseling and guidance with new technologies can help patients and their practitioners make meaningful decisions about turning medical information into actionable clinical knowledge in accordance with personal health care preferences and values.[127] Currently, however, many persons lack access to such services. The principle of justice and fairness suggests finding affordable, cost-effective ways to give all people in need access to informed counseling and related medical care.

Recommendation 5

The principle of justice and fairness requires that all individuals have access to adequate information, guidance, and support in making informed choices about what medical tests to undergo, what kind of information to seek, and what to do with information once received. The principle of justice and fairness also requires affordable access to quality information about incidental and secondary findings, before and after testing, which when coupled with access to care can be potentially lifesaving or life enhancing.

Clinical counseling can be of utmost importance to attaining the best and most equitable health outcomes prior to participating in tests or procedures.[128] Counseling can help assess whether a particular test is necessary given the likely quality and reliability of results, and can highlight any limits professionals face in interpreting these results.

> "How do we convey to [patients] what all this means in a way that doesn't lead them to make a mistake in either potentially dangerous direction? One mistake I am terrified about is a woman is told she doesn't have a high risk of breast cancer so she decides she doesn't need mammograms. That could be a fatal error."
>
> Greely, H., Deane F. and Kate Edelman Johnson Professor of Law, Stanford Law School; Professor (by courtesy) of Genetics, Stanford Medical School; Director, Center for Law and the Biosciences; Director, Stanford Interdisciplinary Group on Neuroscience and Society and its Program in Neuroethics, Stanford Law School; Chair, Steering Committee of the Center for Biomedical Ethics. (2011). Ethics of Emerging Diagnostic and Predictive Tools. Presentation to the Bioethics Commission, February 28. Retrieved from http://bioethics.gov/node/195.

Clinicians, researchers, and DTC companies all operate in a world where some people lack adequate access to quality counseling and health care. More equitable access to quality counseling and care is critically important whenever someone is confronted with health information such as incidental and secondary findings that can carry significant, negative health consequences.

For incidental findings to be managed in an appropriate and ethical way, there must be a health care system available to all that is capable of dealing with medically significant findings, whether discovered incidentally or as primary or secondary findings. This includes support for time afforded to practitioners to discuss with potential recipients how incidental and secondary findings will be handled.

* * *

These overarching recommendations—calling for a robust informed consent process, evidence-based practice guidelines and additional empirical research, additional stakeholder education, and justice in access to health care—provide guidance for the ethical management of incidental and secondary findings across contexts. The following chapters provide context-specific analyses and recommendations that provide additional guidance to clinicians (Chapter 4), researchers (Chapter 5), and DTC providers (Chapter 6).

CHAPTER 4
Ethical Management of Incidental and Secondary Findings in the Clinical Context

In 2004, Carol Krucoff sat for her annual physical. She remembers her primary care doctor performing the routine checks while looking through her medical records. "Let's get your cholesterol checked," advised the doctor, "and you'll need to get a repeat MRI [magnetic resonance imaging test] to monitor that little brain tumor." Carol was stunned. "What brain tumor?" she stammered. The doctor explained to Carol that a previous MRI, conducted when Carol had been in a coma, revealed an abnormality.

About six months earlier, Carol had participated in a marathon in Jamaica and had over-hydrated, inadvertently consuming too much water. In the last mile, she began to feel dizzy as her sodium level fell dangerously low. Just after crossing the finish line, Carol had a hyponatremia-induced seizure and was air lifted for medical treatment. She awoke from a coma four days later in an intensive care unit.

Carol had only a vague recollection of the doctors telling her that they had performed an MRI and had incidentally discovered a small acoustic neuroma. At the time, Carol had not thought of this incidental finding as potentially dangerous; her trauma clinicians had never used the phrase "brain tumor."

After Carol's 2004 annual checkup, she went online to learn more about her acoustic neuroma. Carol researched her options: she could have a surgical removal, undergo radiation therapy, or simply submit to routine observation. After much deliberation, Carol chose to watch and wait. Carol has been watching for nine years—and watching has required commitment and nine MRIs.

Now, says Carol, "I try to completely forget that I even have this little brain tumor. Had I not learned about it as an incidental finding, I would have been blissfully ignorant." But Carol is not certain that blissful ignorance would have been her preference. "If the question [is], do I wish they hadn't told me, my answer is definitely no. If they know, I want to know."

Source: Krucoff, C., Recipient of a finding incidental to clinical care. (2013). Incidental Findings in the Clinic. Presentation to the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission), April 30. Retrieved from http://bioethics.gov/node/1619.

When patients enter their health care provider's office, they often seek preventive care, diagnoses, or relief of specific symptoms. Clinical means of achieving these goals can, however, reveal previously unidentified, potentially asymptomatic, incidental and secondary findings. This chapter considers the practical, legal, and ethical implications of such findings that arise in the clinic, and makes context-specific recommendations.

Practical Considerations of Incidental and Secondary Findings in the Clinical Context

For clinicians and patients, one of the most challenging aspects of an incidental finding is determining what should be done in response.[129] In some cases, clinical investigation of such a finding can lead to a diagnosis and beneficial, perhaps

CASE STUDIES

HYPOTHETICAL INCIDENTAL FINDINGS IN THE CLINIC

An incidental finding with devastating consequences

A 68-year-old man with no vascular risk factors (and no history of smoking) experienced transient weakness on one side of his body lasting 10 minutes. As part of a standard workup for a transient ischemic attack—a warning sign for a stroke—he received a computed tomography (CT) angiogram of the head and neck. The exam was negative for any clinically significant atherosclerosis of the carotid arteries or great vessels leading from the heart, but the study also revealed an unrelated one-centimeter nodule in the left upper lobe of the lung that was then biopsied for concern of malignancy. During the CT-guided biopsy, he suffered a pneumothorax (collapsed lung) followed by a cardiac arrest due to hypoxia, and was left with permanent anoxic brain injury. The pathology report on the lung nodule revealed a benign area of inflammation.

A most useful incidental finding

A 16-year-old high school junior suffered a concussion sustained in a school soccer match. Although he only lost consciousness momentarily—his main recollection was "seeing stars"—over the next week he experienced post-concussive complaints of dizziness, fatigue, and cognitive clouding. An MRI scan of the brain was obtained to search for evidence of a brain injury. No trauma was found, but an unexpected mass was identified. This resulted in neurosurgical resection of an early brain tumor (glioma); complete removal was possible because the tumor was identified at a very early stage. The patient made a complete recovery and, after more than 20 years, has had no recurrence. It is extremely unlikely that cure would have been achieved had the tumor not been detected at such an early, presymptomatic stage.

even lifesaving, treatment.[130] In many other cases, however, further testing reveals that the incidental finding would have had no health consequences if left untreated.[131] Pursuing an incidental finding might require conducting additional diagnostic tests or procedures that expose patients to additional risk, anxiety, or other psychological ramifications.[132] If the finding turns out to have no medical significance, patients undertake these additional risks, including the risk of further incidental findings, without corresponding benefit.

For a variety of reasons, clinicians might be motivated to pursue diagnostic workups of incidental findings even when a clinician's professional judgment suggests that such workup is unnecessary.[133] This motivation could stem, in part, from the prevailing notion that learning more information necessarily means providing better care.[134] Both clinicians and patients can have difficulty accepting this uncertainty, even if certainty is unlikely to be obtained through additional testing.[135] And ignoring an incidental finding or pursuing a "wait and see" course of action, often referred to as "watchful waiting," might be questioned if this decision results in a poor outcome.[136] Clinicians might be motivated by patients and their families who prefer to be "better safe than sorry," without fully understanding that pursuing incidental findings often entails additional risks.[137] Clinicians also might be motivated to err on the side of investigating incidental findings for fear of legal action,[138] even though data on the motivations and rates of litigation do not substantiate these fears.[139] In addition, clinicians might choose to seek secondary findings when suggested by professional guidance, such as the recent recommendations by the American College of Genetics and Genomics (ACMG) that laboratories seek and report a list of actionable genetic variants whenever clinical genomic sequencing is conducted.

"We have a bias toward doing something as opposed to doing nothing. It feels right even if it's wrong, which in many cases it surely is. And our patients almost uniformly want us to do something. Both doctor and patient are enthralled in this overwhelming medical imperative to act. Remaining still—old-fashioned watchful waiting—requires a fortitude that few doctors are able to muster."

Ofri, D., Associate Professor, New York University School of Medicine, Editor-In-Chief, Bellevue Literary Review. (2013). Incidental Findings in the Clinic. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1619.

Pursuing incidental and secondary findings also can have financial costs. For example, the Centers for Medicare and Medicaid Services recently decided not to cover CT colonographies for colorectal cancer in part because of the follow-up costs associated with incidental findings.[140] And recently published cost-effectiveness studies determined that low dose X-ray CT screening for lung cancer in high-risk patients was cost effective even though the studies did not take into account the full costs of incidental findings.[141] The American College of Radiology is incorporating the results of this study into the ongoing development of new clinical practice guidelines.[142] There are, however, few data on the cost effectiveness of following up on many other incidental or secondary findings or the level of benefit conferred to average patients.[143]

Finally, members of the clinical care team must engage in careful communication with regard to incidental and secondary findings. Inadequate communication about a test result or a patient's record can impede decision making concerning such findings. For example, primary care physicians who order imaging scans often rely on radiologists to interpret the scan. Radiological consent might not include information about potential incidental or secondary findings, and radiologists might have little or no contact with individual patients.[144] If clinicians do not specifically request information about incidental findings at the outset, or do not transmit particular patient preferences, radiologists might return an interpretation to the primary clinician without contextualizing the findings in light of a patient's medical or family history or preferences about receiving incidental findings.[145] Moreover, although not unique to the management of incidental or secondary findings, without proper communication among clinicians, patients might be subjected to testing that is broader than necessary, with the attendant possibility of discovering additional findings.[146] Communication among members of the clinical care team and between the clinician and patient is discussed in more detail below in the text surrounding Recommendation 6.

Legal Considerations of Incidental and Secondary Findings in the Clinical Context

There are currently no federal or state statutes that directly address a clinician's duty to return incidental or secondary findings to patients. Medical malpractice

law, however, offers insight into how courts have interpreted a clinician's duty to report incidental or secondary findings, and the potential legal liability a clinician might face for failing to identify and disclose such findings.

Medical malpractice is a legal claim alleging an act or omission by a physician or other health care provider during a patient's treatment that deviates from the standard of care (defined in the legal system as the accepted practice among other clinicians practicing in the same specialty) and that causes injury to a patient.[147] Professional guidelines regarding the management of incidental and secondary findings have the potential to affect the legal standard of care if practitioners adopt them into their practice of medicine.

To date, few reported U.S. medical malpractice cases (as opposed to those settled out of court) have addressed clinician liability for failure to identify or disclose incidental findings.[148] A recent study evaluating this limited body of case law concluded that it is possible that clinicians could face liability for failure to identify or appreciate the significance of an incidental finding, or failure to disclose an incidental finding to the patient or other clinicians, if recognition and disclosure would have prevented or altered the course of future disease.[149] In the 2006 case of *Riley v. Stone*, however, a Rhode Island court found that the defendant neurologist did not breach the standard of care when he failed to further assess an incidental finding that he deemed not to pose a danger to the patient.[150]

Ethical Considerations of Incidental and Secondary Findings in the Clinical Context

The physician-patient relationship encompasses trust, dependency, and the moral aspects of medical decision making.[151] The ethical principles that help guide clinical practice—including respect for persons, beneficence, and justice and fairness—also can be used to ground clinicians' obligations to patients regarding the ethical management of incidental and secondary findings.[152] This analysis also highlights prudent clinical judgment as a central professional virtue that facilitates interpretation and application of these principles in medical decision making.

Respect for Persons

Respect for persons, as implemented in the clinical context, helps ensure that patients are sufficiently informed about tests and procedures to make health care decisions that are consistent with their values and beliefs.[153] The standards by which clinicians have fulfilled their ethical duties have evolved over time, transitioning from the paternalistic model of clinician-centric decision making to a model of shared decision making, which recognizes a patient's ability to make autonomous decisions concerning their medical care.[154] The consent process and the process of shared decision making support patient autonomy by ensuring that patients are informed and enabled to make choices regarding their health care and evaluate health information consistent with their values and beliefs.[155]

Some have argued that respect for persons requires that clinicians disclose all incidental and secondary findings, no matter how clinically insignificant.[156] This approach is consistent with data showing that patients prefer increased access to information, regardless of any anxiety or uncertainty that could result.[157] Others contend that respect for persons does not establish an unbounded duty to provide patients with all possible clinical information; nondisclosure can be justified "by the need to avoid harm to patients, to promote patient welfare, and the practical necessities of everyday medical practice."[158]

The autonomous patient also has a right *not* to know selected information and should be able to exercise this right (to the extent possible). For example, an elderly and frail patient who has undergone several rounds of treatment for cancer thought to be in remission might not want her practitioner to tell her about a mass spotted on a scan conducted for another purpose. Or a patient might not want to know of all findings from large-scale genetic sequencing. Respecting persons means that clinicians, acting in accordance with a patient's best interest and expressed wishes, must use professional judgment to provide information that supports an individual's ability to make medical care decisions—which sometimes includes respecting a patient's desire not to know.

Beneficence

The principle of beneficence, demonstrated in part by appropriate care and concern for a patient's wellbeing, is central to the ethos of physicians and other

health professionals.[159] Beneficence begins with a basic duty to rescue that is applicable to everyone. The duty to rescue is an obligation to come to the aid of those facing dire peril when assistance is easily given.[160] In the clinic, however, the obligation to provide rescue is more robust and applies even when providing rescue is burdensome. Clinicians' expertise makes them more capable of offering help and therefore more responsible for providing it. Their professional commitment requires clinicians to shoulder burdens for their patients far greater than we would expect of those without a preexisting relationship.

Patients entrust clinicians with many aspects of their health, engendering the strong fiduciary obligations that characterize clinical care.[161] A clinician's fiduciary duty entails "[a] duty of utmost good faith, trust, confidence…; a duty to act with the highest degree of honesty and loyalty toward another person and in the best interests of the other person."[162] Non-physician clinicians have the same fiduciary duties. For example, the American Nurses Association's *Code of Ethics for Nurses* states that a nurse's primary professional commitment is to the patient.[163]

"Clinicians have strong fiduciary duties to patients, meaning they have the duty to place the interest of the patient above almost all other competing concerns. Moreover, they have these duties because they possess distinctive knowledge and expertise that patients lack, which patients must rely on in order to preserve or advance momentous individual interests related to the avoidance of suffering [and] preserving and promoting their health and longevity."

London, A.J., Professor of Philosophy, Carnegie Mellon University, Director, Center for Ethics and Policy, Carnegie Mellon University. (2013). Incidental Findings in Research. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1617.

Non-maleficence, beneficence's corollary ethical obligation to "do no harm," requires that clinicians consider any benefit sought in light of the risks incurred. The ethical obligation to do no harm also supports the use of "therapeutic parsimony"—a virtue that calls for selectivity in the choice of interventions.[164] With respect to incidental findings, clinicians must consider whether the risk of harm of pursuing an incidental finding is greater than the risk that the finding presents in the first place. The development of clinical best practices and institutional-level policies allows clinicians to act on their inclination that "doing more does not always mean better care."[165]

Although clinicians have a fiduciary duty to act in a patient's best interest, there are instances in which the beneficent action is unclear or when *not* acting might be best. For example, the question of whether a clinician should disclose a patient's genetic predisposition to Alzheimer's disease—a disease for which there is currently no effective cure and no ability to prevent onset—raises nuanced and difficult questions. Beneficence demands that a physician use professional judgment to determine whether disclosure would do more harm than good for the particular patient, and respect for persons requires that a patient's preferences be ascertained, preferably before testing.

The focus of the principle of beneficence is on the individual patient. The corollary principle of *public* beneficence supports society in its pursuit to secure public benefit and minimize personal and public harm. Public beneficence asks clinicians to facilitate the betterment of health care as a whole. It requires that clinicians consider not only the benefits and harms of disclosing and managing incidental and secondary findings with one patient, but also consider how these actions affect other stakeholders in medical care. For example, when incidental or secondary findings arise in the emergency room setting, clinicians must consider the time and resources needed to manage one patient's finding in light of other patients who require urgent care.[166] In deciding whether to pursue follow-up testing of such a finding, public beneficence might call on institutions to consider the costs of pursuing incidental or secondary findings generally to help ensure the responsible use of medical resources.[167]

Justice and Fairness

The principle of justice and fairness relates to the distribution of benefits and burdens across society.[168] The United States spends more per capita on health care than other countries and also has one of the highest rates of spending growth.[169] The principle of justice and fairness requires that patients with incidental or secondary findings receive resources appropriate to the medical priority of their needs and cautions against using health resources in a profligate manner or without considering other health priorities.[170] Clinicians make decisions every day regarding resource allocation.[171] Best practices that encourage the responsible use of tests and procedures can help clinicians manage health care resources effectively and efficiently.[172]

By choosing interventions to diagnose and manage incidental and secondary findings on the basis of evidence and cost effectiveness, clinicians exercise stewardship in a responsible manner.[173] Individual clinicians can help reduce the unnecessary use of health resources, such as unnecessary follow up or duplicative tests and procedures, by exercising professional judgment and using available guidance.[174] For example, the Choosing Wisely Campaign is an initiative that is co-sponsored by more than 50 professional medical societies that seeks to educate physicians and patients about how to choose the appropriate medical test for a particular patient's circumstances, and how to recognize when a particular test is unnecessary or might cause more harm than good.[175] A common repercussion of discovering an incidental or secondary finding is that an individual can enter into a "chain" of medical interventions.[176] When such tests and procedures are unnecessary, they will at best fail to help, and worse might harm, patients.

Clinicians should also consider the proper use of health resources in their daily activities, including both material resources and their time. While society generally expects clinicians to prioritize their obligations to individual patients, each clinician-patient relationship is situated within a larger health care infrastructure that must attend to the needs of all patients.

When considering how best to manage incidental and secondary findings, clinicians also should assess the finding's urgency in light of the patient's

CASE STUDY

INCIDENTAL FINDING ARISING FROM A CT SCAN

A patient arrived in an emergency department with abdominal pains and a CT scan was ordered, revealing a small nodule on an adrenal gland. Ninety-eight percent of the time these incidentally found nodules are benign. However, medical reference texts state that the standard of care for these nodules is to conduct several complicated tests to rule out cancer. These tests include a 24-hour urinary collection and refrigeration, a prescription that must be taken on an empty stomach at exact times before the follow-up blood test, and additional CT scans—immediately and at 6 months, 1 year, and 2 years out. Describing these tests to a patient might take away a clinician's ability to devote time to discussing the patient's other pressing health concerns—such as the abdominal pain for which the CT was ordered in the first place.

Source: Ofri, D., Associate Professor, New York University, School of Medicine. (2013). Incidental Findings in the Clinic. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1619.

overall health to determine how best to use the time allotted for a particular clinical visit, and should communicate the relative priority of a particular finding given the patient's other health needs. Clinicians and patients must work together to ensure that an incidental or secondary finding does not undermine the best use of a clinical encounter.[177]

Justice and fairness is also a matter of ensuring that patients have appropriate access to care in a way that neither creates nor exacerbates health disparities.[178] Policies for managing incidental and secondary findings should acknowledge patients' differing capacities to access and consume health care resources, and recognize that existing socioeconomic conditions of inequality can act as barriers to patients' access to medical care.

Analysis and Recommendations

When clinicians discover incidental findings, or contemplate seeking secondary findings, their professional judgment must include skilled and insightful deliberation guided by the ethical principles described above: respect for persons, beneficence, and justice and fairness. Application of these principles to incidental and secondary findings in the clinical context leads to the following recommendations.

Consent in the Clinical Context

A primary point of communication between clinicians and patients occurs during the clinical informed consent process, ideally led by the clinician most intimately familiar with the intervention and its possible consequences (e.g., radiologists in the case of imaging).[179] As part of the consent process, clinicians should alert patients that a particular test or procedure could or will give rise to anticipatable incidental and secondary findings. Clinicians should also notify patients about the possibility that unanticipatable findings could arise that lead to additional diagnostic testing or clinical care. The patient should be encouraged to ask questions, state reservations, and express preferences about the return and management of incidental and secondary findings. Clinicians who adopt a policy of seeking and returning secondary findings should ensure that their patients are aware of the kinds of findings that will be sought and disclosed. Clinicians should ascertain and respect patient preferences whenever possible with regard to disclosure of non-primary findings.

One of the arts of clinical communication is to distinguish and focus on the medical information central to the particular clinical encounter. For incidental findings that are of uncertain significance or for which disclosure is unlikely to benefit patients, clinicians can exercise professional discretion in deciding what level of detail, if any, to disclose while still demonstrating respect for patients' self-determination.[180] In fact, often this discretion of detail is what enables patients to process and focus on the most relevant issues, thereby enhancing shared decision making.

Some have argued that these conversations are too burdensome given the time pressures clinicians face.[181] When done properly, however, the informed consent discussion need not be particularly time-consuming and could prevent future testing and patient anxiety—saving clinicians time in the long term.[182]

Recommendation 6

Clinicians should make patients aware that incidental and secondary findings are a possible, or likely, result of the tests or procedures being conducted. Clinicians should engage in shared decision making with patients about the scope of findings that will be communicated and the steps to be taken upon discovery of incidental findings. Clinicians should respect a patient's preference not to know about incidental or secondary findings to the extent consistent with the clinician's fiduciary duty.

There are multiple points at which a clinician's ability to communicate clearly and effectively about incidental and secondary findings is important. Clinicians should alert patients to the possibility of discovering incidental findings, and any secondary findings that will be actively sought, *before* testing occurs so that patients have the opportunity to express preferences regarding their disclosure and subsequent management. While many patients will want their practitioner to tell them about any information discovered, others might not want to learn about incidental or secondary findings. Patients who do not wish to learn about information related to the *primary* purpose of the test should not undergo the test.

On the other hand, if patients wish to opt out of receiving *incidental* or *secondary findings* that are clinically significant, actionable, and of serious importance to their health, then clinicians should exercise discretion.[183]

Clinicians should explain the potential benefits of receiving information about clinically actionable findings. Within certain limitations, clinicians could, on ethical grounds, decline to perform the test and elect to refer the patient elsewhere. Alternatively, clinicians can ethically agree to perform the test but not return any incidental or secondary findings. Clinicians should also inform patients of their obligation to comply with reportable disease statutes in their state.

EXAMPLE IN ACTION

INFECTIOUS INCIDENTAL FINDINGS

Public health considerations underlie state and local laws requiring the reporting of certain infectious diseases. Although subject to some variation, all U.S. state and some local jurisdictions require that selected communicable conditions be reported because of the danger they present to those infected and society at large. U.S. states derive this power from "police powers," which include "the inherent authority of sovereign governments to do what is necessary to protect the health and well-being of its citizens." Incidental findings of infectious diseases are therefore managed by public health officials regardless of context or method of discovery.

Source: Hoffman, R.E., and F.E. Shaw (2013). Legal basis for infectious disease surveillance and control in the USA. In N.M. M'ikanatha, et al. (Eds.). *Infectious Disease Surveillance*, Second Edition (pp. 583-595). Hoboken, NJ: John Wiley and Sons.

Once clinicians discover and disclose an incidental or secondary finding, they must communicate with their patients about various options for additional pursuit of the finding. Clinicians should clearly convey to patients the possible outcomes of investigating an incidental finding, the possibility of discovering additional incidental findings, and the potential benefits and risks of either pursuing or not pursuing the finding. Payment systems should not disincentivize clinicians from taking sufficient time to fully communicate this necessary information to each patient.

In all circumstances, clinicians can ethically filter incidental findings that have no or little clinical significance according to available evidence and decide not to seek them as secondary findings.

* * *

With the increasing emphasis on patient autonomy and shared decision making, it is important to employ effective methods of conveying information about risk.[184] Clinicians can facilitate patient understanding by effectively presenting pertinent facts and data. Both patients and clinicians tend to respond to personal risks emotionally, regardless of the facts, which can affect their decision making.[185] Relaying relevant information in a clear and understandable manner is essential to patient comprehension and effective decision making. In approaching shared decision making in the clinical setting, clinicians must be aware of factors that shape patients' perceptions of risk in order to communicate effectively. Clinicians should give patients enough information so that they comprehend their options, and should also protect patients from unnecessary anxiety produced by misunderstood communication of risk.

Recommendation 7

In communicating difficult to understand information about incidental and secondary findings, clinicians should consider providing patients with decision aids and graphical representations, using population-based evidence, and describing a patient's absolute risk (the chance of any person getting a disease) rather than or in addition to relative risk (whether a person's chance is higher or lower than another's).

Clinicians should consider incorporating graphs and other visual displays to enhance comprehension for risk communication and medical decision making. Accurate graphical displays of numerical and probabilistic health information can assist patients in accessing, processing, interpreting, and acting on numerical health information.[186] It is also critical that clinicians use relevant and understandable numerical evidence to support shared decision making. Accuracy remains an important criterion, as graphs and visual displays can be as misleading as wrong thoughts about risk. When appropriate, numeric assessments of risk should be provided as absolute risk instead of or in addition to relative risk, as relative risk can be easily misinterpreted (e.g., a patient's risk of future disease might be twice as high as that of the general population but an individual patient's risk might still be extremely low). For example, telling a patient that an incidental or secondary finding increases relative risk of disease 10-fold can sound alarming, but if this is based on a change in absolute risk from one in a million to one in 100,000, the patient is likely

to be reassured by having this relative risk placed in an absolute perspective. Similarly, population-based evidence can help patients understand their overall risk compared with the population as a whole.

Empirical Data in the Clinical Context

Little is known about the cost effectiveness of tests and procedures that generate incidental and secondary findings.[187] One study suggested that while diagnostic testing constituted only five percent of hospital costs and 1.6 percent of Medicare costs, the findings from these tests influenced 60 to 70 percent of downstream decisions.[188] If these tests are not likely to result in health benefits for the patient, they are not an effective use of funds.

Seeking cost effectiveness—an outcome that takes into account both the costs and health outcomes of alternative intervention strategies[189]—in laboratory tests or diagnostic procedures is laudable, and in many cases also might help address the issue of ever-rising health care costs. While there have been some cost-effectiveness studies regarding incidental findings, they have generally been limited in scope. For example, some studies have analyzed the follow-up costs from incidental findings in CT colonography, but they have almost always excluded the cost of subsequent surgical procedures, in-patient hospitalizations, psychological impacts, long-term consequences, or estimates of net health benefit to patients.[190]

> "[I]t is important to realize that there is no clear evidence, to date, that obtaining a diagnostic evaluation of any specific incidental finding improves patient outcomes. What is certain is that follow-up of incidental findings increases health care costs. Research is needed to document outcomes associated with specific incidental findings to provide an evidence base on which these decisions can be made."
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> Berland, L.L., Chair, American College of Radiology. (2013, July 5). Comments submitted to the Bioethics Commission.

One decision that clinicians make is whether to use sequential, discrete diagnostic tests or instead order a battery of related tests, perhaps based on a desire to save time. A clinician might order a battery of tests when a patient complains of generalized symptoms, and the physician wishes to investigate several diagnostic avenues at once to ascertain the likely cause quickly and efficiently. Discrete, targeted testing can take more time when the diagnostic process involves eliminating probable causes of symptoms sequentially.

Ordering a battery of tests instead of discrete tests, however, can increase the likelihood of discovering incidental and secondary findings.

Clinicians might also order bundled tests—tests that are grouped together by insurers or laboratories for cost or efficiency reasons. Bundled tests are thought to be less expensive, and are often encouraged by laboratories or health care institutions.[191] In the case of bundled tests, physicians often do not have the option of choosing discrete tests as an alternative—the decision to bundle tests is made at the insurer, laboratory, or institutional level.

If bundled tests or a battery of tests give rise to incidental or secondary findings that would not have been discovered using discrete targeted tests, the total costs of these tests, measured both in terms of cost effectiveness and in terms of potential harms to patients, actually might be higher.

Recommendation 8

Federal agencies and other interested parties should study the comparative benefits to patients and the cost effectiveness of using bundled tests or a battery of tests versus conducting sequential, discrete diagnostic tests.

Few studies elucidate the difference, both in terms of financial costs and medical benefits to patients, between conducting bundled tests or a battery of tests versus sequential, discrete diagnostic tests.[192] Compounding the problem is that payers do not always consider the cost effectiveness or quality of laboratory testing in their reimbursement decisions.

To inform individual clinicians, as well as support strong clinical practice guidelines, researchers should conduct reliable comparative- and cost-effectiveness analyses. Empirical evidence assessing the comparative effectiveness of discrete, sequential diagnostic testing versus batteries of tests should be developed. As discussed below in Recommendation 9, clinicians should aim to practice "diagnostic elegance" and "therapeutic parsimony," choosing tests selectively to confirm or help narrow potential diagnoses. The alternative, testing broadly and ordering a battery of tests to generate possible avenues of diagnostic inquiry, can be viewed favorably as a more efficient way of obtaining information about a particular patient's condition. But ordering a broad battery of tests can also generate incidental and secondary findings that lead to additional diagnostic tests and procedures that expose patients

to potentially unnecessary risks. Empirical data about the comparative effectiveness of these two approaches can enable clinicians to make informed decisions in ways that are most beneficial to patients. These analyses should take into account the overall cost to the patient of following up on an incidental or secondary finding—including the medical risks of downstream diagnostic techniques and procedures, anxiety, pain, inconvenience, and lost time—to better characterize the net benefits and harms.

Cost-effectiveness studies should assess the long-term costs, along with the risks and benefits to patients, from the use of a "bundled tests" approach versus a "sequential discrete diagnostic tests" approach. Although bundled tests are presumed to be more cost effective (and are generally bundled by laboratories or insurers precisely for their presumed cost effectiveness), bundled tests return several results instead of one, increasing the possibility of incidental and secondary findings, which could lead to additional testing to diagnose any findings that are discovered. This additional testing has financial, medical, and psychological costs as well as benefits that should be considered in any comparison of the two approaches.

> "More weight will need to be given to practice guidelines and comparative-effectiveness analyses in which we consider, among other things, costs—not only the actual cost of administering the tests, but also the harms that may follow from the 'follow up,' particularly for invasive interventions."
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> Clayton, E.W., Craig-Weaver Professor of Pediatrics; Professor of Law and Director, Center for Biomedical Ethics and Society, Vanderbilt University. (2011). Challenges in Translating Whole Genome in the Clinic. Presentation to the Bioethics Commission, February 28. Retrieved from http://bioethics.gov/node/196.

Evidence regarding comparative benefits to patients of tests that yield incidental and secondary findings and the cost effectiveness of performing such tests can inform laboratory and payer practices and policies regarding efficient bundling of tests, and can aid clinicians in deciding whether to order a battery of tests rather than sequential, discrete tests.[193] Such cost-effectiveness evidence can help inform health policy, including the practices and policies of hospitals and insurance providers.[194]

Clinical Judgment in Managing Incidental and Secondary Findings

While empirical analysis is critical to informing cost-effective care choices, it is the art of medical decision making that translates data, education,

professional guidance, and personal experience into good clinical care. Prudent judgment, understood through Aristotle's concept of *phronesis* (or practical wisdom), constitutes a "capstone" virtue, linking intellectual virtues—such as those that make for good scientists—with the moral character traits—such as compassion, trustworthiness, and a sense of justice—that make one a particularly good caregiver.[195] Exercising professional judgment is a deliberative process combining formal or "book" knowledge of a professional domain with contextual understanding gained through experience.[196] Although professional judgment is required for every decision that involves considering competing values, principles, or virtues, there is no specific formula by which clinicians identify the right action.[197]

Many of the attributes that constitute respected clinical judgment can be cultivated and enabled through classroom and clinical education. Clinical educators can enable students to learn how to employ professional judgment founded not only on medical textbooks and lectures but also by emulating other physicians, apprentice learning, and through their own experiences in clinical decision making.[198] This judgment reflects a capacity to make decisions and advise patients under conditions of uncertainty.

Clinicians can minimize the likelihood of incidental findings by engaging in selective diagnostic testing. They can do this by emphasizing thorough communication with patients to better understand symptoms and help narrow the list of potential diagnoses before ordering diagnostic tests. In this way, clinicians can use diagnostic tests to confirm or eliminate specific possible causes of symptoms.

Recommendation 9

Medical educators, both in the classroom and clinic, should continue to cultivate "diagnostic elegance" and "therapeutic parsimony" amongst practitioners—ordering and conducting only tests and interventions necessary for addressing health concerns related to their patient.

An absence of diagnostic protocols, prognostic uncertainty, and varying patient preferences can complicate effective clinical decision making. For example, an oncologist providing palliative care for a terminally ill patient might incidentally discover an unrelated health condition for which treatment is available. The oncologist would rely on clinical judgment, coupled with expressed patient

preferences to decide whether to pursue the incidental finding considering the possible psychological and physical harms of additional tests, and the discomforts of the anticipated course of treatment, in light of the patient's current medical condition and prognosis.

> "[E]ven…clinicians…may not all be cognizant of [a] particular condition [that can be found incidentally]. They will be [focused on] what they're looking for, breast cancer for instance, but they may not [see] the clinically significant incidental findings…that are staring them in the face when they do next generation sequencing—including both whole genome and whole exome."
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> Knoppers, B., Director, Centre of Genomics and Policy; Canada Research Chair in Law and Medicine, McGill University. (2012). International Perspectives on the Return of Individual Results and Incidental Findings. Presentation to the Bioethics Commission, August 1. Retrieved from http://bioethics.gov/node/740.

Clinical practice guidelines can be helpful in establishing standards regarding how clinicians ought to handle incidental and secondary findings, but guidelines do not mandate standard of care or substitute for a medical professional's independent judgment. Rather, adherence to current professional guidelines is voluntary, and many guidelines emphasize that their purpose is to assist clinicians' exercise of professional judgment with regard to particular clinical situations.[199] For example, although recent ACMG recommendations suggest that laboratories seek and return certain secondary findings, clinical circumstances will influence a clinician's professional judgment and shared decision making about whether to adhere to such guidance.

Clinicians should also be mindful of factors that could lead to increased diagnostic testing, including compensation incentives, industry influences, and hindsight bias (or the inclination to see events that have already occurred as more likely to occur than they were before they took place). For example, under a fee-for-service reimbursement system, clinicians might have financial incentives to conduct further tests or procedures, whereas clinicians under a salary or a capitated reimbursement system might have financial incentives to minimize further testing.[200] Particular medical specialties might be prone to conducting additional testing, especially those that provide in-office ancillary services.[201] Clinicians should be vigilant against becoming unduly biased by industry influences (e.g., diagnostic laboratories and medical device companies) or by various forms of remuneration or professional support from industry representatives.[202]

Clinicians' duties include the obligation to review all of the clinical data generated, and not to bracket or ignore potential incidental findings.[203] Clinicians' fiduciary duty suggests that they ought not filter certain results exclusively in order to evade moral responsibility. Clinicians should not blind or limit themselves from discovering incidental findings to avoid further accountability.

* * *

Another important tool that clinicians have to enhance their exercise of professional judgment is the ability to rely on evidence-based standards, including recommendations from professional organizations. One critical area in which professional organizations make recommendations is preventive screening programs—programs in otherwise healthy populations that aim to identify undiagnosed diseases and conditions before symptoms develop.[204] Examples of preventive screening programs include screening for various cancers—including breast, cervical, colorectal, and prostate cancers—and other diseases such as diabetes mellitus (type 2 diabetes), human immunodeficiency virus (HIV), and high blood pressure.[205]

For example, deliberations about the effectiveness of the use of CT in lung cancer screening are ongoing. A 2012 study found that practitioners detected the incidental finding of coronary artery calcification in approximately 50 percent of individuals,[206] and recent data from the National Lung Cancer Screening Trial indicate that CT lung cancer screening might be cost-effective for high-risk patients. Accordingly, the U.S. Preventive Services Task Force recommended annual screening of certain patients determining that there was sufficient net benefit even in light of potential harms associated with incidental findings.[207]

This type of evidence-based deliberation is critical to ensuring that patients have access to preventive screening programs that offer health care benefits appropriately calibrated to any foreseeable risks—including those that can arise from incidental and secondary findings.

Recommendation 10

Professional and public health organizations should produce evidence-based standards for proposed screening programs that take into account the

likelihood that incidental findings will arise. Professional organizations should provide guidance to clinicians on how to manage these incidental findings.

The implementation of evidence-based standards in screening programs would assist physicians in exercising clinical judgment about any findings that might arise. Proposed screening programs that take into account the possibility of incidental findings enable clinicians to exercise their professional judgment in deciding whether to conduct a screening test or procedure for a particular patient.

For example, one type of test employed in screening programs is CT colonography; a CT examination of the abdomen and pelvis can reveal incidental "extracolonic" findings as well as non-cancer colonic disorders.[208] Due in part to the unknown benefits and harms of detecting and evaluating incidental findings, the Centers for Medicare and Medicaid Services issued a non-coverage decision for this technology.[209] Better data and evidence-based standards would aid payers like the Centers for Medicare and Medicaid Services in making coverage decisions, in addition to assisting physicians in exercising judgment about which screening procedures to conduct.

Conclusion

A combination of ethical principles and practitioner virtues and duties—instilled during clinical education, informed by updated clinical practice guidelines, and operationalized through the use of prudent clinical judgment—forms the basis for managing incidental and secondary findings in the clinical context. Having a plan for managing the incidental and secondary findings expected to arise from a test or procedure that is disclosed to and discussed with patients in a process of shared decision making will help clinicians navigate the ethical management of incidental findings towards greater patient benefit.

CHAPTER 5
Ethical Management of Incidental and Secondary Findings in the Research Context

Sarah Hilgenberg will never forget the summer of 2002. She had finished her second year as a clinical researcher in neurology at Massachusetts General Hospital and was about to begin her first year at Stanford University School of Medicine. Young and healthy, Sarah looked forward to her future.

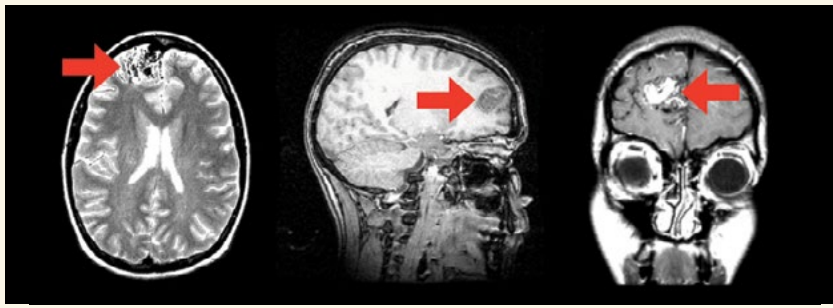
As part of her medical school orientation, Sarah spent four days camping in the Sierra Nevada Mountains with her new classmates. A few weeks later, Sarah received an email from one of the camping leaders, a graduate student studying functional magnetic resonance imaging (fMRI). Two research participants had canceled their sessions for an upcoming research study and the camping leader wondered if any group members would be interested in having their brain scanned while performing a memory task. Sarah volunteered to help.

The next day, Sarah went to the campus imaging center and participated in the fMRI study. Later that day, her phone rang. The fMRI researchers had found an anomaly on her scans. Sarah rushed to the emergency room for further evaluation. Ultimately, the doctors concluded that Sarah had an arteriovenous malformation, an abnormal connection between arteries and veins in her brain. They recommended that she undergo removal of the mass.

Sarah chose to stay in medical school during this time. Pursuing treatment of the incidental finding on her fMRI scan gave Sarah a new perspective: that of a patient. She remembers, "I was learning firsthand the material taught in class, the vulnerability of the body and, in particular, of my brain."

Fortunately, Sarah's surgery was successful and she has recovered well. She notes: "I believe I've had the best outcome I probably could have had…. In 2011, my husband and I had a daughter…who is the most special person in our lives. I was so unbelievably thankful that I no longer had [this malformation] in my brain during childbirth as I learned this is a common time for one to bleed."

Sarah is now a pediatric hospitalist, dealing occasionally with incidental findings as a practitioner rather than as a patient. But she will undoubtedly remember her time as a patient and the incidental finding that might have saved her life.



As indicated in the image above, researchers incidentally discovered an arteriovenous malformation in Sarah Hilgenberg's brain on a scan during a memory research study.

Source: Hilgenberg, S., Recipient of a finding incidental to research. (2013). Incidental Findings in Research. Presentation to the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission), April 30. Retrieved from http://bioethics.gov/node/1617.

The diversity of the research enterprise presents a challenge when establishing best practices for managing incidental and secondary findings. Researchers conduct studies in a variety of settings, use an array of methods and procedures, possess a wide range of qualifications, set recruitment goals of various sizes, draw from a variety of funding sources, and form researcher-participant relationships that vary in depth and duration. Despite this diversity, researchers and institutions need clear, consistent, and practical guidance about the ethical duties owed to research participants with respect to incidental and secondary findings.

A defining feature of research, as distinct from clinical care, is that participants contribute to the creation of generalizable knowledge; they take on potential risks of harm for the benefit of others. Unlike clinical care, in which potential harms are weighed against direct benefits to the individual patient, research participants might not receive individual direct benefit commensurate with risks assumed. The ethical management of incidental and secondary findings in research therefore differs from the clinical context because participants cannot routinely expect the same degree of personal benefit that patients customarily receive. This chapter details the practical, legal, and ethical considerations of the management of incidental and secondary findings that arise in the research context and makes context-specific recommendations.

"Research is the social enterprise of generating new knowledge. It serves the legitimate social purpose of supplying the information base necessary to understand human conduct; human health; to create, assess, and improve interventions; and ultimately, in the context of medical research, to improve the ability of health systems to understand and to meet the needs of the populations that they serve. In contrast, clinical care is the social enterprise of bringing to bear current knowledge, expertise, and interventions to address the health needs of individual patients."

London, A.J., Professor of Philosophy, Carnegie Mellon University, Director, Center for Ethics and Policy, Carnegie Mellon University. (2013). Incidental Findings in Research. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1617.

Practical Considerations of Incidental and Secondary Findings in the Research Context

A thorough analysis of the ethical management of incidental and secondary findings in the research context must take into account the complex practical realities of researchers' activities. Some features unique to the research context are both practically and ethically relevant to any guidance developed, and help delineate the scope and stringency of researchers' obligations.[210]

For instance, researchers are involved in a broad range of researcher-participant relationships that vary in depth and duration.[211] Researchers who have long-standing relationships with their participants might be better able to ascertain participants' preferences with respect to incidental and secondary findings and to more appropriately return results; some clear and dire findings that potentially could save lives might, however, be less influenced by interpersonal relationships.

Researchers also have a wide range of expertise. While some researchers are clinicians with relevant subject matter expertise, other investigators lack the expertise needed to detect and interpret various anomalies. For example, a psychologist engaged in research using brain scans might know how to detect the neural correlate of a behavior central to the research, but lack the diagnostic skill set necessary to detect many incidental findings.

Participant preferences can influence a researcher's ethical obligation to return incidental and secondary findings. One study found that up to 90 percent of research participants wanted all research results returned to them, regardless of whether the results were clinically actionable.[212] When considering whether and how to return findings, researchers should be aware of the possibility and potential consequences of exacerbating the therapeutic misconception—a

participant's mistaken conflation of the goals of research with the goals of clinical care, and the consequences that might flow therefrom.[213] Participants in imaging research, for example, commonly believe that a qualified professional will review all research scans.[214] Elsewhere, a majority of research participants involved in brain imaging research who did not expect a clinician to be involved nevertheless expected researchers to detect any existing brain abnormality.[215]

Some have suggested that researchers' ethical obligations to return incidental or secondary findings depends on features of the finding itself.[216] These features can include:

- analytic validity (the accuracy and precision of the finding);[217]
- clinical validity (the causal association of the finding with pathology);
- clinical actionability (the extent to which a finding can be acted upon in clinical decision making);
- clinical or reproductive significance (the extent to which a finding has medical implications for one's self or offspring);[218] and
- the magnitude, or seriousness, of potential harm.[219]

Congruent with the ethical principle of beneficence, findings that indicate the possibility of serious harm to a participant support a policy of returning incidental and secondary findings, as disclosure might help forestall or prevent harm. By contrast, disclosing a finding that lacks clinical or reproductive significance might cause more harm than benefit if disclosing the finding causes anxiety for the participant with no ability to reduce foreseeable harm.

To the extent that researchers *do* have ethical duties to disclose and manage incidental and secondary findings, researchers should discharge these duties in a timely manner, particularly if findings require urgent action and if doing so can minimize anxiety to participants.[220] If a great deal of time has passed since the participant's active role in research, researchers must consider whether disclosing incidental or secondary findings is still advisable given the potentially dated nature of the information (e.g., an anomaly seen on an imaging test might have already been discovered and treated).[221]

Researchers also must remain mindful of the costs associated with returning incidental and secondary findings. Confirming findings, obtaining

appropriate interpretation, returning findings in a responsible manner, providing referrals, and conducting follow up all impose costs.[222] If patient-specific results from tests on biological specimens are going to be returned to participants, most agree that they should be analyzed in or confirmed by a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA, which establishes standards for clinical laboratory testing).[223] The costs of discovering, interpreting, and disclosing incidental or secondary findings might interfere with the ability to complete research projects and thereby jeopardize the production of generalizable knowledge.

CASE STUDY

BIOBANK RESEARCH

Biobank research raises practical considerations distinct from other research settings. A recent study reviewing biobank policies found that half of the surveyed biobanks address the return of incidental findings, but few suggest that they should be returned. Often, the data stored in biobanks are de-identified such that researchers cannot readily link the data to particular individuals. De-identification makes the return of incidental findings much more difficult. Biobank researchers often lack access to the code that facilitates re-identification, and in many cases agreed that they would not attempt re-identification. A recent study of incidental findings in biobank research estimated the cost to be $1,322 per disclosure, including the cost of retesting archived DNA samples, providing genetic counseling, contacting participants, and conducting follow up.

"Because one biorepository may supply tissue specimens to hundreds of investigators, the return of incidental findings to participants from the secondary research that follows is impracticable. Hence the biorepository community views any such requirement with great concern. Biorepositories serve as an intermediary between patients from whom specimens are collected and processed, and investigators to whom specimens are provided and who generate research results. Most biorepositories do not have access to secondary research results, and have no infrastructure for the return of incidental findings to participants. Developing such an infrastructure, including informatics necessary to support the return of incidental findings would be extremely costly for biorepositories, most of which have marginal funding."*

Sources: Wolf, S.M., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genetics in Medicine*, 14(4), 361-384; Johnson, G., Lawrenz, F., and M. Thao. (2012). An empirical examination of the management of return of individual research results and incidental findings in genomic biobanks. *Genetics in Medicine*, 14(4), 448; Christensen, K.D., et al. (2011). Disclosing individual CDKN2A research results to melanoma survivors: Interest, impact, and demands on researchers. *Cancer Epidemiology, Markers and Prevention*, 20, 522-529; Bledsoe, M.J., et al. (2013). Return of research results from genomic biobanks: Cost matters. *Genetics in Medicine*, 15(2), 103-105.

* Zaayenga, A., President Elect, International Society for Biological and Environmental Repositories (ISBER). (2013, July 8). Comments submitted to the Bioethics Commission.

Legal Considerations of Incidental and Secondary Findings in the Research Context

No federal law, federal regulation, or state law directly addresses the return of research results or incidental or secondary findings.[224] The Common Rule, formally titled the "Federal Policy for the Protection of Human Subjects," is a set of regulations governing research with humans that establishes protections central to the ethical treatment of research participants. Among other things, the Common Rule generally requires that the 18 federal departments and agencies that sponsor research with humans have an informed consent process that adequately notifies participants of the potential benefits and risks of the study. If discovering incidental or secondary findings is viewed as either a benefit or a risk, the Common Rule could require disclosure about the possibility of such findings and any policy for their return.[225] The Common Rule could also require disclosure of particular incidental or secondary findings as "significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation."[226]

The Health Insurance Portability and Accountability Act's (HIPAA's) Privacy Rule grants individuals a right to access certain aspects of their medical information upon request.[227] This right to access, however, only relates to information from "covered entities" that store personal health information in a designated record set. Covered entities include health insurance plans; health care providers, such as hospitals; doctors, nurses and other practitioners; and health care clearinghouses—third parties that are contracted by hospitals to process billing claims and perform other functions.[228] Participants enrolled in research studies conducted at covered entities could therefore have access under HIPAA to medical information ascertained through the research process.[229]

CLIA provides a set of federally mandated standards for all laboratory testing involving human biological specimens. Because CLIA does not apply to research laboratories that "do not report patient specific results for the diagnosis, prevention or treatment of any disease," research laboratories often choose not to obtain CLIA certification.[230] There is currently disagreement about whether research findings discovered in non-CLIA-certified laboratories can be returned to participants. A National Institutes of Health National Heart, Lung, and Blood Institute working group suggested that if results

are disclosed as research findings as opposed to clinical findings, institutions should be able report results and avoid the need for CLIA certification.[231] Other groups, such as the National Research Council and the Institute of Medicine, have interpreted the regulations to mean that any reporting of individual results subjects a laboratory to the CLIA requirements.[232] This debate leaves researchers uncertain about their obligations under CLIA.

It is possible that researchers could face potential liability for failing to return incidental or secondary findings, although no court has specifically addressed the issue of a researcher's legal obligation to return such findings.[233]

Ethical Considerations of Incidental and Secondary Findings in the Research Context

The discovery of incidental or secondary findings gives rise to ethical obligations owed by researchers to participants. Approaches to managing such findings are generally grounded in the traditional research ethics principles of respect for persons, beneficence, and justice and fairness.[234] Approaches can similarly be grounded in the principle of intellectual freedom and responsibility, which recognizes the social value of scientific research and the attendant requirement that researchers take responsibility for their contributions.[235]

Respect for Persons

Respect for persons recognizes an individual's fundamental capacity for self-determination and protects individuals from being used merely as means to an end. Participants' decisions to take part in research involves a choice to open up aspects of their private lives to researchers—to grant researchers permission to intervene with their bodies or lives in ways that would be illegitimate without consent. Henry Richardson expands upon this concept in his recent book *Moral Entanglements: The Ancillary-Care Obligations of Medical Researchers*.[236] To demonstrate respect for persons, researchers must communicate the fundamental aspects of their research to participants so that participants can make autonomous decisions about whether to enroll in research. Researchers also demonstrate respect for participants by informing them about the possibility of discovering incidental or secondary findings and the plan for their disclosure or management.[237]

Informed consent is one mechanism for respecting persons, but it is not the exclusive means by which researchers display due consideration for participants and their interests. Researchers should ascertain at the outset what participants prefer to know—or not to know—about incidental or secondary findings. Acting in accordance with participants' expressed preferences, to the extent possible, recognizes that participants are capable of autonomously determining whether this information should be considered a benefit or a burden.

> "Respect for persons or autonomy is ensured when we engage in an honest and fulsome informed consent process with the intent of promoting knowledgeable decision making by the subjects. Respect for persons or autonomy, however, does not promote a subject's 'right' to specific research results. Rather, the autonomy principle should ensure that potential subjects know what to expect about return of research results prior to deciding whether to participate in the research."
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> Gasson, J., Senior Associate Dean for Research, and Dubinett, S., Associate Vice Chancellor for Research, University of California, Los Angeles. (2013, July 5). Comments submitted to the Bioethics Commission.

Communicating to participants in advance the scope of the incidental or secondary findings that researchers plan to disclose—including letting participants know that, in some circumstances, certain findings might not be disclosed at all—can display respect for individual autonomy by permitting participants to assess the ramifications of participation.[238]

Beneficence

Beneficence requires that researchers demonstrate concern for the wellbeing of others,[239] and could stem, at least in part, from the trust implicit in participants allowing privileged access into their private lives.[240] Researchers therefore might have obligations to act in ways that benefit participants stemming from this privileged access.[241] The ethical counterpart of beneficence is non-maleficence, or the ethical imperative to "do no harm." Non-maleficence does not, however, require that no harm ever befall participants. Rather, this ethical principle warns against avoidable harm and requires an evaluation of whether the prospective benefits of an action outweigh the risks. Beneficence and its corollary non-maleficence therefore require that researchers and IRBs evaluate and justify the risks and benefits of particular approaches to managing incidental and secondary findings.

With respect to incidental and secondary findings, beneficence calls upon researchers and institutional review boards (IRBs) to consider whether the benefits of disclosing a finding outweigh the risks of disclosure. For example, disclosing an incidentally discovered brain malformation that has the potential to cause long-lasting damage but that is otherwise treatable could allow a participant to avoid future harm, thereby providing benefit. By contrast, disclosing an incidental finding for which no preventive or positive action can be taken has the potential to cause anxiety and distress with no corresponding medical benefit. One example of such a finding is the disclosure of misattributed paternity.

The avoidance of harm also provides a strong basis for exercising restraint when considering whether to disclose incidental or secondary findings that have the potential to lead participants into a chain of potentially risky follow-up tests and procedures.[242] Whether researchers ethically should disclose a finding that is not clinically actionable is a nuanced question, requiring consideration of practical matters, patient preferences, and a weighing of the benefits and harms. Researchers must be mindful of differentiating between the harms of returning an incidental or secondary finding and any harm posed by the underlying condition itself.[243]

Some have suggested that incidental findings be categorized based on the benefits and risks of disclosing the particular finding.[244] Under this model, there would be three tiers of findings to be disclosed: findings that generally should be disclosed, findings for which disclosure is ethically permissible, and findings that should not be disclosed. When the benefits of disclosure outweigh the risks, the finding should be disclosed; one such example is a *BRCA* mutation, a clinically actionable indication of an increased risk for breast or cervical cancer. When the benefit of disclosure *might* outweigh the anxiety and other associated risks, depending on participant preferences and other factors, disclosure is ethically permissible, as in the case of Huntington's disease, which is not clinically actionable but might have reproductive significance. In these cases, researchers should use discretion regarding whether to disclose these findings in consultation with IRBs or other consultative bodies. And when the finding would lead to distress and anxiety without corresponding benefit, the finding should not be disclosed.[245] One such example would be a very small lung nodule in a non-smoker, a finding that is

exceedingly likely to be benign, and for which follow-up investigation would cause anxiety and potential health risk.[246]

Researchers also have duties of public beneficence, or duties to society more broadly.[247] Public beneficence involves supporting and promoting research activities and practices that offer the potential to improve the public's wellbeing by advancing the state of generalizable knowledge.[248] In deciding whether to return incidental or secondary findings, researchers should consider the costs of returning such findings in light of their duties to individual research participants and to the production of generalizable knowledge.

Justice and Fairness

The principle of justice and fairness requires the equitable distribution of benefits and burdens of research.[249] Decisions about whether to return incidental or secondary findings—including whether to allocate time and resources to interpreting, assessing, and disclosing findings—involve determinations about the allocation of the benefits and burdens of research. Researchers who disclose incidental and secondary findings might benefit some participants (who are able to effectively address health concerns) while burdening others (who are not able to address such concerns). The principle of justice and fairness calls upon researchers and society at large to take into account how incidental and secondary findings policies shed light on the allocation of scarce research resources. Allocating research resources to returning large numbers of incidental or secondary findings could burden the research enterprise and the ability to create generalizable knowledge.

Incidental and secondary findings implicate the principle of justice and fairness in another way—by making visible the dire and unmet needs of others. For example, those who lack adequate access to health care might be more likely to have undetected health conditions, and might therefore have readily discoverable incidental or secondary findings.[250] As a result, incidental or secondary findings in research can make existing health disparities more visible.

Intellectual Freedom and Responsibility

Intellectual freedom is the liberty to engage in sustained and dedicated creative intellectual exploration—an activity necessary to further scientific and technological progress.[251] The principle of intellectual freedom and

responsibility is particularly pertinent to the research context, where the advancement of individual and collective capacities for investigation coincides with the responsibilities that attend novel developments in knowledge, science, and technology. Intellectual freedom gives researchers the latitude necessary to engage and persevere in dedicated intellectual exploration for the good of society.[252]

The principle of intellectual freedom and responsibility consists of two parts: the liberty to use creative capacities in scientific investigation, and the corresponding responsibility that researchers have to conduct themselves professionally.[253] Researchers must take responsibility for their actions—acknowledging the profound trust placed in them both by research participants and by society. Researcher responsibilities include complying with all policies governing research, and adhering to the ideals of responsible conduct of research.[254] A corollary principle of regulatory parsimony calls for "only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursing the public good."[255] In this spirit, policies concerning the return of incidental or secondary findings should avoid excessively restrictive rules that might jeopardize and hinder progress in science, medicine, and health care.

Analysis and Recommendations

Existing scholarship regarding incidental and secondary findings in research reflects both the research community's deep concern for participants' wellbeing, and an emerging consensus regarding what is ethically required, permissible, and impermissible. The Bioethics Commission therefore makes the following recommendations to guide the ethical management of incidental and secondary findings in the research context.

Consent in the Research Context

In response to the trust imparted to them, researchers owe society and research participants obligations to design and implement research in a responsible manner.[256] During the informed consent process, researchers should describe the types of incidental and secondary findings that might arise to ensure that participants are as informed as possible. This includes, but is not limited to, disclosing anticipatable incidental findings, any deliberately sought secondary findings, and the possibility of unanticipatable incidental findings.

Researchers should also clearly communicate to participants the plan for disclosing and managing anticipatable incidental findings as well as any possible secondary findings, and the distinction between research and clinical care. This communication is essential to ensure that participants understand what to expect as a result of their decision to participate in research. Clarity with respect to whether and how researchers will disclose anticipatable and unanticipatable incidental findings, as well as any secondary findings that are deliberately sought, can help sustain public and participant trust in the research enterprise.

Recommendation 11

During the informed consent process, researchers should convey to participants the scope of potential incidental or secondary findings, whether such findings will be disclosed, the process for disclosing these findings, and whether and how participants might opt out of receiving certain types of findings.

If researchers plan to inform participants of certain types of incidental findings, they should decide in advance how to respect the wishes of those who choose to opt out of receiving incidental findings. If researchers have ethical objections to allowing participants to opt out of receiving clinically significant, actionable, and lifesaving findings, they need not enroll such individuals in their research study. Delineating such exclusion criteria for study enrollment will minimize this type of ethically challenging situation once the research protocol is underway. For example, disclosing a secondary finding of a genetic predisposition to malignant hyperthermia—a condition associated with severe, life-threatening reactions to certain kinds of anesthesia—could be lifesaving, and a researcher reasonably might believe it is unethical to enroll a potential participant who does not want to know this information.

Alternatively, given that participants have the right to opt out of research at any time,[257] if researchers do not object to allowing participants to opt out of receiving incidental findings—and participants are well informed regarding what opting out could mean for their health and wellbeing—researchers may enroll such participants in the research. In the event a researcher discovers a potentially lifesaving unanticipatable incidental finding for a participant who has opted out of receiving incidental findings, the investigator should seek advice from an IRB about whether and how to disclose it.

In 2010, a National Institutes of Health National Heart, Lung, and Blood Institute working group addressed the issue of whether researchers could override a participant's expressed preference not to receive an important finding. The working group's views were split. It recommended that the researchers honor participants' expressed preferences not to know, but recognized that "there may be exceptional circumstances in which the evidence of potential harm is so great, and the potential for reducing the harm associated with the finding is so compelling that the principal investigator should confer with the IRB on whether there is an ethical basis to override the wishes of the participant."[258] The Bioethics Commission agrees with the importance of planning ahead for incidental findings, providing clear exclusion criteria should participants disagree with the researchers' plans regarding returning or not returning such findings, and notifying participants during informed consent so they are clear about the implications of participating.

Planning for Incidental Findings in Research

Given that certain findings are predictably associated with a particular modality or type of research, researchers have a duty to anticipate such incidental findings—whether common or rare—to the extent possible. Researchers should develop a plan to manage *anticipatable* incidental findings based on a careful balancing of the risks and benefits of disclosure, along with evidence about the analytic and clinical validity of the findings and their clinical or reproductive significance, in addition to considering actively seeking them as secondary findings. Researchers should submit their proposed plan for the ethical management of incidental findings to an IRB for review and approval. IRBs then would be responsible for assessing the ethical adequacy of the plan.

Even for incidental findings that fall outside of researchers' expertise, researchers should nevertheless be familiar enough with the anticipatable incidental findings associated with the modalities used in their research to formulate and describe a plan for how these findings will be managed. Researchers could, for example, propose adding members to the research team who have sufficient expertise to manage the range of anticipatable incidental findings. Researchers could also propose relying on research ethics consultants

or IRBs if there is uncertainty as to the advisability of disclosing a particular finding to a participant.

If practical or logistical constraints prevent a researcher from searching for, interpreting, or disclosing incidental findings, the researcher can propose a plan for IRB review that states that certain types of anticipatable incidental findings will not be returned. Disclosing a plan for managing incidental findings, and allowing for nonparticipation if a prospective participant disagrees, appropriately respects an individual's ability to make autonomous and informed decisions about whether to participate in research.

Recommendation 12

Researchers should develop a plan to manage anticipatable incidental findings, including but not limited to those findings known to be significant and clinically actionable (and, when relevant, analytically valid and clinically valid). The plan should be reviewed and approved by an institutional review board.

Even with an IRB-approved plan for managing anticipatable incidental findings, researchers nevertheless might discover *unanticipatable* incidental findings. The unexpected nature of these findings makes it difficult to ascertain at the outset what responses might be required. Despite, and indeed because of, this uncertainty, researchers should have a process in place ahead of time to manage these unanticipatable incidental findings as well.

When researchers are uncertain whether an unanticipatable incidental finding might have clinical or reproductive significance, researchers should seek out qualified clinical or diagnostic experts for consultation. Consultation with subject matter experts can help researchers resolve uncertainty, determine the significance of the finding, and develop and implement an informed and appropriate response.[259]

Recommendation 13

Researchers should develop a process for evaluating and managing unanticipatable findings. The plan should be reviewed and approved by an institutional review board. During the informed consent process, researchers should notify participants about the possibility

of unanticipatable incidental findings, including lifesaving incidental findings, and the plan for their management. Researchers who discover an unanticipatable incidental finding of concern should assess its significance, consulting with experts as appropriate.

An incidental findings management plan should include specific information regarding the method of disclosure. For example, researchers might wish to disclose the existence of genetic incidental findings in the presence of a genetic counselor to assist participants in understanding the finding's significance.[260] Nonclinical researchers also might involve clinicians in discussions with participants about incidental findings, or researchers using materials obtained from biobanks conducting secondary analysis might involve the original researcher.

The plan for managing incidental findings should also include a description of the research team's responsibilities following disclosure of such a finding. In some cases, researchers might provide basic educational information about the nature of the finding, advice regarding how to seek care from a clinician or specialist, or guidance about obtaining health insurance to secure treatment. If a clinical specialist is required, researchers should provide the participant with a referral when possible. Disclosure of an incidental finding, however, does not transform a research relationship into a clinical one.

For certain kinds of research, disclosure of incidental findings is difficult, if not impossible. One such example might include biobank research using de-identified samples. But even in these instances, researchers should demonstrate thoughtful deliberation in developing and justifying their plan of nondisclosure. Researchers should not design their research protocols with the explicit purpose of avoiding discovery of incidental findings. Researchers should have sound scientific, practical, and ethical reasons to use de-identified samples, to employ non-experts (such as graduate students) to read scans or interpret research results, to conduct research in resource-poor settings where follow-up care is difficult, or to not analyze data that were collected. Such choices can and should be informed by the availability of resources, the study's scientific objectives, the accuracy of the data obtained or analysis required, and the protection of participants.

No Duty to Look for Secondary Findings in Research

Researchers' obligations of beneficence raise questions about whether and to what extent researchers might have a duty to look for secondary findings. While some researchers have research funding to look for secondary findings, this will not be true for many of those conducting valuable research endeavors. Prioritizing a duty to look for secondary findings over the creation of generalizable knowledge has the potential to undermine the research enterprise.

> "I worry that the ethical drive to return incidental findings in research, however good some of the outcomes may be…turns the research enterprise into a proxy clinical enterprise."
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> Green, R., Associate Director for Research, Partners HealthCare Center for Personalized Genetic Medicine, Associate Professor of Medicine, Division of Genetics, Brigham and Women's Hospital and Harvard Medical School. (2013). Ethical Challenges of Emerging Technologies. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1618.

Recent recommendations issued by the American College of Medical Genetics and Genomics (ACMG) about large-scale genetic sequencing articulate an ethical "duty to look" for a given set of secondary findings in the *clinical* context.[261] The ethical obligations of clinicians and researchers are, however, distinct. Whereas clinicians have strong fiduciary duties to act in the best interests of patients, researchers have obligations to their participants and to society. Both society at large and participants engaged in research have a vested interest in completed research that furthers scientific knowledge.

Because researchers have obligations both to research participants and the creation of generalizable knowledge, their obligations to deliberately seek secondary findings that are outside the primary purpose of their research are less extensive than obligations of clinicians. Researchers have no general duty to actively look for secondary findings. Researchers are not, however, precluded from pursuing, disclosing, and managing secondary findings should they so choose. Any plan to deliberately seek secondary findings should be reviewed and approved by an IRB and should be disclosed to prospective research participants.

Recommendation 14

Researchers should consider carefully the decision to actively look for secondary findings. In certain circumstances, with approval from an institutional review board, researchers can justifiably adopt a plan that includes looking for selected clinically significant and actionable secondary findings. Approved plans should be disclosed to prospective participants during the informed consent process.

Even without an ethical duty to actively look for secondary findings, researchers could, in some circumstances, justifiably adopt a plan to look for secondary findings. For example, a research team investigating the genetics of a particular community could decide—but would not be obligated—to implement the advice of a community advisory board that recommends looking for a particular variant if requested by a participant, even if the variant is outside the aims of the research. By acknowledging the community's interest and simultaneously completing their research, researchers could advance both the public and individual components of beneficence. Also, while researchers do not have an affirmative duty to look for secondary findings, this does not dilute the importance of developing a plan for managing those that they find and of educating participants about the details of this plan.

Conclusion

An established set of ethical principles—informed by the practical realities of research—form the basis for the ethical management of incidental and secondary findings in the research context. Respect for persons requires that researchers be open and transparent about the procedures used in conducting research, and that they communicate to participants in advance the possibility of discovering incidental and secondary findings. Obligations of beneficence require that researchers consider and justify the potential risks and benefits involved in disclosing such findings. The principle of justice and fairness calls upon researchers to strive to respond appropriately and professionally to incidental and secondary findings. Finally, the principle of intellectual freedom and responsibility grants researchers the liberty to use their creative capacities in scientific investigation, while simultaneously expecting researchers to exercise their freedom responsibly. Together, these ethical

principles require that researchers have a plan for the ethical management of incidental and secondary findings that arise in research—put in place ahead of time and clearly communicated to potential participants—that is vetted and supported by an IRB or expert review structure.

CHAPTER 6
Ethical Management of Incidental and Secondary Findings in the Direct-to-Consumer Context

DIRECT-TO-CONSUMER GENETIC TESTING

Thirty-four year old Jackie, an employee of a biomedical research laboratory, was curious about her predisposition to various diseases so signed up for a medical risk report from 23andMe, a direct-to-consumer genetic testing company. She knew that cancer, alcoholism, and bipolar disorder ran in the family. Jackie and her brother Alex* wanted to know more, so the siblings sent saliva samples into the company and agreed to go over their results together.*

Jackie and Alex read through their reports online, and were not surprised by any of the results. At the end of the report, the system prompted them to opt in to an additional service that could link users to close relatives who had also submitted genetic information. Jackie and Alex both opted in to the service—and learned of a result that took them by surprise. The results stated that Alex was Jackie's uncle.

Jackie posted this odd finding on a forum for questions and discussion about the company's results. The community of users told Jackie that the system had detected that Jackie and Alex shared one-quarter of their DNA. While full siblings share 50 percent of their DNA, more distant relationships, such as uncle and niece, grandfather and granddaughter, or half siblings share only 25 percent of their DNA. This meant that Alex and Jackie could be uncle and niece, grandfather and granddaughter, or half siblings.

Jackie and Alex were confused and distressed by the news. Jackie asked their mother about the result, and her mother admitted to an affair that resulted in Jackie's birth. Jackie described the experience as surreal, saying, "I looked in the mirror and thought, who is this person?"

23andMe informs its users that its genetic testing service can reveal misattributed paternity and other surprises about biological relationships that could "evoke strong emotions" or "alter your worldview." Despite being warned about this risk, Jackie was shocked to discover this anticipatable incidental finding.

*These names have been changed.

Sources: Engber, D. (2013, May 21). Who's your Daddy? The perils of personal genomics. *Slate*. Retrieved from http://www.slate.com/articles/health_and_science/science/2013/05/paternity_testing_personal_genomics_companies_will_reveal_dna_secrets.html; 23andMe. (n.d.). Terms of Service [Webpage]. Retrieved from https://www.23andme.com/about/tos/.

Members of the general public have increasingly gained access to medical tests and procedures outside of traditional clinical or research settings. Situated at the intersection of medicine and business, direct-to-consumer (DTC) companies offer the public additional mechanisms for obtaining health-related information. Thus far, the full breadth of DTC activities, and their associated ethical considerations, have been relatively underexplored in the literature. This chapter provides an overview of the practical, legal, and ethical considerations facing providers of DTC testing with regard to incidental and secondary findings.

Practical Considerations of Incidental and Secondary Findings in the Direct-to-Consumer Context

A growing number of tests are available DTC.[262] These include genetic testing, whole body scans, computed tomography (CT) colonography, non-medical fetal ultrasound, and cholesterol tests.[263] Some DTC tests, such as at-home pregnancy or HIV tests, provide only the information explicitly sought, and so generally do not give rise to incidental or secondary findings.[264] Some DTC tests, including whole body scans intended to find any and all anomalies, are unlikely to give rise to incidental or secondary findings because the test has the broad purpose of revealing all discovery findings; by design, almost nothing is incidental. Still other DTC tests—including fetal ultrasounds and DTC genetic tests (both discussed in more detail in *Chapter 2: Modalities and*

EXAMPLE IN ACTION

MOBILE MEDICAL APPLICATIONS

One example of an emerging form of DTC testing is mobile medical applications. These products offer medical information and diagnosis through applications (or "apps") on smart phones and tablet computers. While some mobile medical applications simply deliver general medical information, others function more like medical devices. Some applications, for example, act as diagnostic tools using only the built-in capabilities of the smart phone or tablet, such as programs that allow users to take images of skin lesions to check for melanoma. Unlike many other DTC services, the return of information from mobile medical applications is frequently automated and does not permit the exercise of individual discretion.

Sources: U.S. Food and Drug Administration (FDA). (2013). Mobile Medical Applications – Guidance for Industry and Food and Drug Administration Staff. September 25. Retrieved from http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf.

Probable Incidental and Secondary Findings)—have the potential to generate incidental and secondary findings.

A number of practical considerations affect the ethical management of incidental and secondary findings in the DTC context. One critical consideration is a consumer's motivation for undertaking DTC testing. Some choose DTC testing services, such as full-body scans, that otherwise might not be available through routine clinical care. Others choose DTC testing because, given the rising costs of co-payments and insurance deductibles, it can be less expensive than similar tests offered in the clinic.[265] Individuals also might undergo DTC testing to avoid having particular results entered into their medical records.[266] And still others use DTC services for entertainment or education; they might simply be curious about health-related or ancestry information.[267]

The level of medical expertise available at DTC testing companies varies widely, with implications for the quality of information consumers can expect to receive. While some companies employ many types of specialists, others employ technicians who do not have expertise in identifying, interpreting, or returning incidental and secondary findings.[268] Even DTC companies that have experience identifying incidental and secondary findings might be unable to adequately contextualize findings due to a lack of additional relevant medical information, such as a family history, that is generally available in the clinic.[269]

Legal Considerations of Incidental and Secondary Findings in the Direct-to-Consumer Context

Individual states have adopted laws regulating or prohibiting DTC services although, as of yet, no state laws directly regulate the return of incidental or secondary findings. According to a 2007 survey, 25 states and the District of Columbia permit DTC testing without any restrictions, 13 states prohibit all DTC testing, and 12 states permit DTC testing only for targeted categories of tests.[270] In a few states, DTC testing can occur only with the authorization and supervision of a physician, bringing it more in line with clinical care.[271] Many states also have consumer protection laws and agencies that regulate the marketing of consumer goods and services.[272]

Several federal agencies regulate specific aspects of DTC testing, though there is not yet a coherent framework for regulating these enterprises. The U.S.

Food and Drug Administration (FDA) is charged with ensuring the safety and effectiveness of medical devices for approved use, but generally does not have authority to regulate how medical devices are used in practice. For example, FDA regulates the safety and effectiveness of X-ray CT machines[273] and, in a statement, FDA noted that the benefits of performing a preventive full-body CT on healthy individuals is questionable.[274] But because FDA lacks the authority to regulate how devices are used, the federal government does not have a way of preventing companies from offering these tests. However, FDA recently initiated regulatory enforcement of DTC genetic tests.[275]

> "With the whole body [scan], that's where you really get into this gray zone between practice of medicine, where a government entity may regulate the machine, but then state law to a greater or lesser extent regulates the use of that machine."
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> Javitt, G., Counsel, Sidney Austin LLP; Research Scholar, Berman Institute of Bioethics, Johns Hopkins University. (2013). Incidental Findings and Direct-to-Consumer Genetic Testing. Presentation to the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission), April 30. Retrieved from http://bioethics.gov/node/1620.

As the agency with primary responsibility for implementing the Clinical Laboratory Improvement Amendments (CLIA), the U.S. Centers for Medicare and Medicaid Services (CMS) has regulatory jurisdiction over DTC laboratory testing.[276] CLIA establishes quality standards for the accuracy and precision of all laboratory testing; it does not, however, guarantee clinical validity or actionability, nor does it impose an obligation to explain the findings that might result from a particular test. Thus, CLIA does not play a direct role in the management of incidental or secondary findings (see *Chapter 5* for a more in depth discussion of CLIA).

The U.S. Federal Trade Commission (FTC), tasked with preventing unfair or deceptive acts or practices in or affecting commerce, also has regulatory authority over DTC advertising and promotion.[277] "Unfair" acts or practices include those that injure consumers, violate established public policy, or are unethical or unscrupulous.[278] "Deceptive acts or practices" include things such as false oral or written representations, or the use of bait and switch techniques.[279]

Even outside the realm of regulatory agencies, other types of law could influence a DTC provider's management of incidental and secondary findings. For example, contract law could play a role in determining the scope of a DTC provider's *legal* obligations. When consumers purchase a health-related test

> "There can be incidental findings [in the DTC context] too. [These findings are] incidental to the contractual arrangement—an arrangement which allows people to opt out [of] finding certain kinds of information. So there may be very important kinds of information [that the DTC companies are] holding that [are] not part of the contract...."
>
> Donaldson, T., Mark O. Winkelman Professor of Legal Studies; Director, Zicklin Center for Research in Business Ethics, The Wharton School of the University of Pennsylvania. (2013). Incidental Findings in the Direct-to-Consumer Context. Presentation to Bioethics Commission, April, 30. Retrieved from http://bioethics.gov/node/1620.

through a DTC provider, the parties enter into a contract for services.[280] In most—if not all—cases, there is a written agreement between the parties that specifies the services that consumers agree to purchase. This document also might describe the types of information that consumers will receive. Even if the terms and conditions specify the tests and results consumers purchase, courts might look at other representations made in companies' advertising, and could find that consumers are entitled to additional results.[281]

Various tort law claims could also be asserted against DTC testing companies but there is, as yet, no case law directly related to this point. DTC companies potentially could be held liable for negligence if they cause harm to consumers by failing to use due care in conducting a test or reporting test results.[282] Finally, DTC companies could face liability for failure to adequately warn or instruct if they do not adequately communicate the risks and limitations of a test in a manner accessible to consumers.[283]

Ethical Considerations of Incidental and Secondary Findings in the Direct-to-Consumer Context

The ethical principles articulated throughout this report—respect for persons, beneficence, justice and fairness, and intellectual freedom and responsibility—must be interpreted in light of private industry's role in providing health information, as well as the economic nature of the relationships between providers of DTC testing and consumers. DTC providers interact in both the business and medical realms, and could find themselves subject to the ethical principles pertinent to business transactions as well as those of medical care. Such ethical guidelines are interpreted in the DTC context in accordance with the principle of regulatory parsimony, suggesting only as much oversight as is truly necessary to ensure responsible business practices.

Respect for Persons

Respect for persons recognizes an individual's fundamental capacity for self-determination—which also is considered a cornerstone of DTC testing. DTC testing enables consumers to exercise greater control over what they know about themselves. Respect for persons also recognizes that individuals have the right to form contracts with others in a free society, so long as such exchanges are not actively contrary to the public good.[284] Autonomous transactions are premised on particular conditions, including that both parties are informed about the nature of the exchange and free from coercion that would effectively force participation in the transaction. In general, the principle of respect for persons is fostered when both parties engage in voluntary and informed consent to the exchange[285] and, with respect to the return of incidental or secondary findings, should include an understanding about how DTC companies intend to disclose and manage such findings.

Beneficence

Beneficence requires that individuals consider and act to advance another's wellbeing. Every individual has an ethical duty to act when confronted with an individual in dire peril, particularly when doing so imposes minimal burden and can prevent or alleviate harm.[286] In the DTC context, disclosure of clinically actionable and significant incidental and secondary findings might fall within this basic duty to warn. Given that DTC providers have a relationship with consumers, and that those with clinical expertise who provide DTC testing retain some fiduciary duties even for tests conducted outside of the clinic, the duties of DTC providers could extend even beyond this minimal duty to warn.[287] By gaining access to and intervening in consumers' lives on a commercial basis, and by virtue of providers' superior knowledge and skills, DTC professionals have responsibilities to respond appropriately to the consequences of their services.[288]

Non-maleficence, a corollary of beneficence, directs DTC companies returning incidental and secondary findings to refrain from doing so in ways that could cause undue harm. The principle of non-maleficence does not impose a prohibition on any harm resulting from private transactions—as a society, we allow people to purchase goods and services that might harm them provided that consumers agree to assume these risks knowingly and

voluntarily. For example, although driving a car carries a risk of accidental injury, people are allowed to purchase and drive cars. Likewise, although exposure to radiation has the potential to cause harm, competent adults can nevertheless knowingly accept this risk in return for the perceived benefits of undergoing a particular DTC imaging test.

Justice and Fairness

The principle of justice and fairness calls upon all stakeholders to consider the reasonableness and legitimacy of the claims of groups or individuals to receipt of goods or fair treatment to which they are entitled.[289] To that end, justice and fairness requires consideration of whether it is reasonable for consumers to expect that DTC companies will return incidental and secondary findings even if not explicitly delineated in a contract.

Intellectual Freedom and Responsibility

The principle of intellectual freedom and responsibility enables consumers and DTC providers to exercise their individual and collective creative potential in morally responsible ways.[290] This principle has two parts: intellectual freedom, and the related duty to manage this freedom responsibly. The exercise of intellectual freedom is expressed through the innovation and ingenuity necessary to make advances in the development and provision of DTC testing services. DTC providers also have a corresponding responsibility to conscientiously manage incidental and secondary findings.

The corollary principle of regulatory parsimony calls for only as much oversight as is truly necessary.[291] This principle suggests adopting regulations that are needed to establish business practices consistent with a just, fair, secure, and safe society but that are not unduly restrictive or counterproductive.[292] In the DTC context, this principle calls attention to the diverse number of agencies currently responsible for oversight of various DTC activities that nevertheless lack policies that specifically address incidental or secondary findings. While current regulations might need to be modified or specified to ensure that consumers receive safe and reliable information, the principle of regulatory parsimony requires policy makers to consider how new regulations will affect the industry. In the DTC setting, parsimonious regulations could provide both the necessary protections for potential consumers and avoid overly burdensome compliance requirements.

Analysis and Recommendations

With this general analysis in mind, the Bioethics Commission makes the following recommendations for the ethical management of incidental and secondary findings in the DTC context.

Consent in the Direct-to-Consumer Context

DTC testing can offer individuals a means through which they can exercise self determination, including by providing increased access, reduced cost, and greater confidentiality of health information. But the benefits of DTC services are contingent upon the quality of the testing and analyses, and the informed and voluntary nature of the transaction. To enable consumers to make responsible and informed choices regarding DTC testing, consumers must be told what these procedures entail, including the possibility of incidental and secondary findings. Information provided before selecting a DTC procedure can assist consumers in deciding what services are worth pursuing.

To willingly undertake the risks of DTC transactions, individuals must be aware of the consequences of any DTC transaction, which include the potential discovery of incidental and secondary findings. Consistent with respect for persons, DTC providers should provide clear and comprehensible information about anticipatable incidental and secondary findings. Accurate information and decision making support, both before and after the transaction, is essential to establish consumers' capacity to exercise self determination regarding whether to undertake DTC testing.

> "[T]here are ways to communicate the implications of this information, even to lay people, but it takes a tremendous amount of effort and curation of the scientific literature and thoughtfulness around how you present the information. It's expensive to return the information in a responsible way."
>
> Mountain, J., Senior Director of Research, 23andMe. (2013). Roundtable Discussion. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1621.

Although some consumers seek out DTC testing as an alternative to clinical care, clinicians and DTC providers owe different ethical and practical duties to patients and consumers. Clinicians owe stringent fiduciary duties to patients, which entail an obligation to act in furtherance of the patient's best interests. Non-clinician DTC providers have less stringent duties, including duties that

might be limited or circumscribed by contract. Consumers should be made aware of these distinctions prior to consenting to undergo DTC testing.

Recommendation 15

Direct-to-consumer companies should provide consumers with sufficient information about their services to enable consumers to make informed decisions regarding purchasing their product. Companies should clearly communicate the scope of procedures and the types of findings that the companies could or will discover and disclose, as well as any findings that they know in advance will not be disclosed.

DTC companies must inform consumers considering their services about the procedures and results included in the commercial arrangement. Among the information needed by consumers is an understanding of the anticipatable incidental findings commonly associated with particular modalities and any secondary findings that will be deliberately sought. If certain results are not returned according to company policy or contractual agreement, this must be disclosed to consumers as well. For example, the DTC genetic testing company 23andMe provides a list on its website of the conditions it will not return.[293] A company's policy not to return certain information should be made clear during the consent process. This practice ensures that consumers are fully informed about the nature of the results they can expect and the results they should not expect.

Government Regulation in the Direct-to-Consumer Context

From air bags and seatbelts to the proper construction of cribs, the government has responsibility for ensuring the safety of certain products and services offered to consumers.[294] As a matter of policy, society has chosen to impose oversight to place legitimate limits on the principle of *caveat emptor* or "buyer beware."[295] The primary goal of this oversight is to establish consumer protections—to ensure that companies make good on both explicit and implicit guarantees that the goods and services proffered are suitable for the purposes for which companies sell them.[296] Federal and state governments can also provide citizens with assurance that DTC companies are conducting business in a transparent and responsible manner.

As discussed above, a variety of government agencies have partial oversight over DTC activities. This patchwork of oversight indicates the need to assure

consumers that DTC providers are engaging in responsible business practices, particularly with respect to the disclosure of incidental and secondary findings. State governments generally are responsible for regulating the practice of medicine. Accordingly, state and federal governments, working together, should be vigilant in monitoring and regulating the safety and reliability of health-related DTC products and services.

Recommendation 16

Federal agencies should continue to evaluate regulatory oversight of direct-to-consumer health services to ensure safety and reliability. State governments also should adopt regulations that ensure a consistent floor of protections for consumers who purchase direct-to-consumer testing.

Policy makers at the state and federal level should examine existing regulations governing DTC services to identify gaps in and barriers to ensuring the safety and reliability of DTC testing. Policy makers should consider adopting regulations governing disclosure of incidental and secondary findings. Policy makers at the state and federal level should remain mindful of the principle of regulatory parsimony, limiting restrictions on the ability to freely engage in commercial transactions only to the extent necessary to prevent serious harm.

Industry-Wide Best Practices in the Direct-to-Consumer Context

The DTC market is relatively new and growing, and the technologies used are often still evolving. Given the diversity in the DTC industry, and the evolving practices employed by DTC companies, DTC companies are uniquely positioned to understand the nature of their own industry. This knowledge could enable DTC companies to develop best practices that are consistent with relevant ethical principles.[297] For example, DTC providers who discover clinically actionable incidental or secondary findings that have health implications could provide consumers with educational information about the nature of the finding, advice about how best to seek care from a clinician or specialist, or even a referral to a clinician who could assist in the management of the finding. If companies adopt voluntary best practices, such best practices could become standard expectations for consumers who choose to undergo DTC testing, giving other companies incentive to adopt and implement these practices, thereby leveling the playing field.

While the creation of voluntary industry-wide best practices is an important step toward ensuring accountability in this emerging industry, self-regulation raises a number of concerns, including conflicts of interest. Self-regulation, therefore, might be insufficient to protect consumer interests. When there is not universal adoption of voluntary industry standards, or if voluntary best practices are inadequate, federal regulation might be needed to prevent companies from avoiding ethical obligations.

These guidelines could be supplemented or supplanted by binding rules crafted by federal or state entities with jurisdictional authority over DTC testing. The process could, for example, follow the precedent set by the Pharmaceutical Research and Manufacturers of America (PhRMA) voluntary best practices have become mandatory in several jurisdictions through incorporation into state law.[298]

EXAMPLE IN ACTION

THE PhRMA CODE

In 2002, PhRMA drafted a voluntary code of conduct to govern best practices for interactions between pharmaceutical companies and health care professionals. This code seeks to ensure that relationships between pharmaceutical representatives and health care providers are designed solely to benefit patients and improve the practice of medicine. Although PhRMA's code is voluntary, the principles and best practices that it encourages became mandatory in several states through incorporation into state law. California, for example, requires all pharmaceutical companies to demonstrate compliance with the code.

Source: Pharmaceutical Research and Manufacturers of America (PhRMA). (n.d.). Ethical relationships with health care professionals are critical to our mission [Webpage]. Retrieved from http://www.phrma.org/code-on-interactions-with-healthcare-professionals; PhRMA. (2009). 105 CMR970.000: Pharmaceutical and Medical Device Manufacturer Conduct. Retrieved from http://policymed.typepad.com/files/mass-code-of-conduct---final-3-11-09.pdf; Cal. Health & Safety §§ 119400-119402 (Deering 2005).

Recommendation 17

Direct-to-consumer companies should aid in the creation of industry-wide best practices concerning the management of incidental and secondary findings. These best practices should include when and how such findings will be disclosed and standards for referral to necessary clinical services. Direct-to-consumer companies should make these "best practices" publicly available to encourage broader adoption.

Voluntary industry-wide best practices can be developed by collaboration among companies and through professional organizations whose members work in the DTC industry. Some professional organizations have issued ethical guidelines for members who are employed by DTC companies. The American Medical Association Council on Ethical and Judicial Affairs, for example, issued a report on DTC imaging services that included recommendations about the responsibilities of physicians employed by DTC imaging companies.[299] The American Institute of Ultrasound in Medicine has also issued a statement about the ethical obligations of members of its profession who are working in the DTC context.[300]

DTC companies should develop best practices regarding disclosure of incidental findings and when secondary findings should be deliberately sought, including the types of findings that ought to be disclosed and the methods for communicating these findings. For particularly sensitive findings, DTC companies could adopt certain procedural safeguards. As an example, a DTC company might require that consumers pass through several layers of information on its web portal to access highly sensitive results.[301] This type of procedural safeguard is one way, absent the availability of comprehensive genetic counseling that might be standard in a clinical setting, that DTC companies could communicate findings that have the potential to cause confusion or anxiety.

DTC companies also should develop best practices for facilitating access to clinical care or other counseling for consumers grappling with the consequences of sensitive disclosures. For example, Inherent Health, a DTC genetic testing company offers a one-on-one appointment with a licensed, board certified genetic professional—a service that is included in the cost of the test.[302]

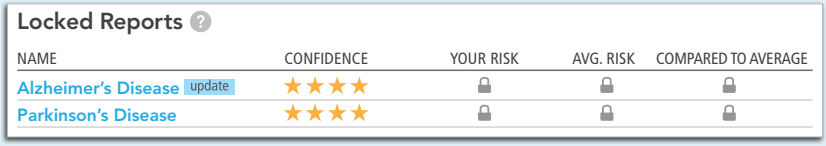
Finally, because DTC providers are involved in widely varied practices, from full body scans to highly sensitive laboratory assays, each of these modalities might need to develop separate voluntary industry-wide best practices. The overarching ethical principles of respect for persons, beneficence, justice and fairness, and intellectual freedom and responsibility should remain consistent throughout.

EXAMPLE IN ACTION

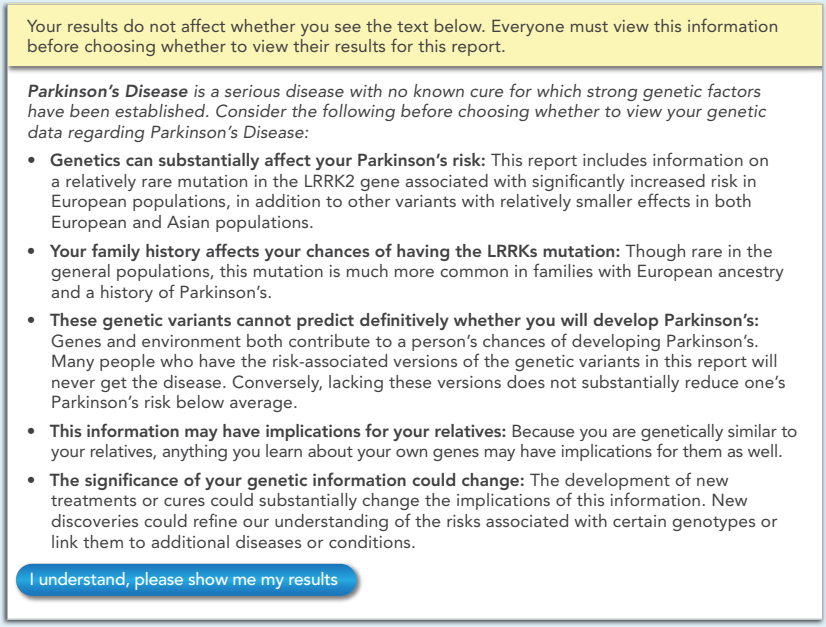
23andMe CONSENT

23andMe, a leading DTC genetic testing company, informs its customers that they might receive unexpected information in their results. In its "Terms of Service," 23andMe alerts its customers, before purchase, that a resulting finding "may evoke strong emotions and has the potential to alter your life and worldview. You may discover things about yourself that trouble you and that you may not have the ability to control or change (e.g., your father is not genetically your father, surprising facts related to your ancestry, or that someone with your genotype may have a higher than average chance of developing a specific condition or disease). These outcomes could have social, legal, or economic implications."

In addition, customers must opt in to view particularly sensitive information in "locked reports" that are not initially displayed on their results page.



Before selecting a "locked report," customers are provided with additional information about the nature of the information without seeing their individual results.



Source: 23andMe. (2013). Terms of Service: Risks and Considerations Regarding 23andMe Services [Webpage]. Retrieved from https://www.23andMe.com/about/tos; Mountain, J. Senior Director of Research, 23andMe. (2013). Incidental Findings: A 23andMe Perspective. Presentation to the Bioethics Commission, April 30. Retrieved from http://bioethics.gov/node/1620.

Conclusion

The challenge of incidental and secondary findings in the DTC context highlights a complex professional relationship that is still developing. The Bioethics Commission recognizes that a thorough ethical analysis must be responsive to the development of new ways for citizens to access information with medical implications. Applying the principles of respect for persons, beneficence, justice and fairness, and intellectual freedom and responsibility in this context indicates that consumers, the government, DTC professionals, and society all share responsibility for ensuring that incidental and secondary findings are responded to in an ethically appropriate manner. A combination of explicit ethical requirements and voluntary development of industry-wide best practices offers the most promising prospects for both DTC companies and private consumers.

CHAPTER 7
Conclusion

This report, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*, has focused on the ethical management of incidental and secondary findings that arise in the clinical, research, and direct-to-consumer (DTC) contexts. The Bioethics Commission also recognizes that incidental and secondary findings can arise in circumstances that do not fit neatly into one of these three contexts and that new situations will evolve that we do not yet imagine. The principles, ethical analyses, and recommendations set forth in this report are intended to guide practitioners in a variety of contexts, current and future.

The ethical principles do not themselves provide explicit mandates about what must be done. Rather, they provide guidance regarding factors that should be taken into account when determining how best to manage incidental and secondary findings. Interpretation and application of these principles can assist professionals in crafting informed, reflective, and ethical responses to incidental and secondary findings in any context.

Incidental findings are challenging because they might, but do not always, have important implications for an individual's health and wellbeing. When the health and wellbeing of individuals is at stake, society has a duty to protect and promote health and safety. To advance these aims, practitioners must be aided by the best available evidence and by clear, yet flexible, guidelines concerning the management of incidental and secondary findings. Policies pertaining to such findings should ensure that practitioners give potential recipients appropriate information about the possibility, likelihood, and consequences of incidental and secondary findings sufficient to enable informed decision making before the start of a test or procedure.

There are many obligations concerning the ethical management of incidental and secondary findings that are context specific. For example, in the clinical context, the fiduciary duty is dominant and requires that clinicians act in the best interest of their patients. In the research context, although researchers are not fiduciaries of participants, they nevertheless owe ethical obligations arising, in part, from moral entanglements based on privileged access to private medical information. The DTC context, situated at the intersection of the business and medical realms, requires consumer protections that extend beyond mere *caveat emptor* or "buyer beware."

Although the issue of incidental and secondary findings has been considered by several groups focused on concerns that are context- and modality-specific, the ethical obligations associated with the discovery, disclosure, and management of such findings have not been comprehensively considered across contexts and modalities. This report seeks to fill this void. In *Anticipate and Communicate*, the Bioethics Commission concludes that in any setting, potential recipients should be properly informed about the possibility of incidental or secondary findings before the start of a test or procedure. Practitioners should also recognize the potentially life-changing nature of certain incidental or secondary findings, and should take care to minimize harm when disclosing these findings. Practitioners and potential recipients benefit from empirical evidence about the likelihood of incidental and secondary findings arising from a particular test or procedure. And everyone—practitioners and recipients alike—can benefit from broader, more inclusive discussions about the ethical concerns, and associated practical and legal considerations, raised by incidental and secondary findings.

ENDNOTES

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[39] Ibid.

[40] Ibid, at 98.

[41] Ibid.

[42] Wolf, S.M., et al., *supra* note 3, at 219. [Emphasis added].

[43] PCSBI, *supra* note 5, at 8. [Emphasis added].

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[62] Aristotle, *supra* note 19; Pellegrino, E.D., and D.C. Thomasma, *supra* note 18.

[63] Beauchamp, T.L., and J.F. Childress, *supra* note 7.

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[66] Beauchamp, T.L., and J.F. Childress, *supra* note 7.

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[81] Gliwa, C., and B.E. Berkman, *supra* note 34, at 36. ("Genomic science is still in its infancy, and the amount we know about the relationship between genomic data and human disease is dwarfed by the amount we do not yet know.").

[82] These are the kind of actions J.S. Mill distinguished as "other-regarding behavior." According to Mill's harm principle, individual freedom is limited by potential consequences for others: "[T]he principle requires liberty of tastes and pursuits; of framing the plan of our life to suit our own character; of doing as we like, subject to

such consequences as may follow: without impediment from our fellow-creatures, so long as what we do does not harm them…" Mill, J.S. (2003). *On Liberty*. D.B. Bromwich and G. Kateb. (Eds.). New Haven, CT: Yale University Press, pp. 89, 139.

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[85] Green, R.C., et al., *supra* note 35, at 565.

[86] Ibid, at 569.

[87] Genetic Testing Laboratories Inc. (n.d.). Health Testing. Retrieved from http://www.gtldna.com/HealthTesting/DNA-Predisposition-Testing.htm; Easy DNA. (n.d.). Genetic Predisposition Health Testing: Your Future Health is in Your Genes. Retrieved from http://www.easy-dna.com/genetic-predisposition-dna-testing.html.

[88] Mountain, J., *supra* note 54.

[89] Ibid.

[90] "That's the key thing I want to mention here. We've added reports. We started with 13. Now we have over 240. So if you got tested in 2007, you would have an increasing number of reports based on that. So that's part of the model." Ibid.

[91] Volk, M.I., and P.A. Ubel. (2011). Less is more: Better off not knowing. *Archives of Internal Medicine*, 171(6), 487.

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[94] See, e.g., Walk-in Lab. (n.d.). Order Tests Online [Webpage]. Retrieved from http://www.walkinlab.com/category.

[95] The "Comprehensive Wellness Profile" and the "10 Most Important Tests" offered by DirectLabs are bundled blood tests. DirectLabs. (n.d.). 10 Most Important Tests [Webpage]. Retrieved from https://www.directlabs.com/OrderTests/tabid/55/language/en-US/Default.aspx.

[96] Medical imaging contributes to approximately 50 percent of the overall radiation dose to the U.S. population, up from 15 percent in 1980; the increase in CT scans are the largest contributor to this increase. Brenner, D.J., and H. Hricak. (2010). Radiation exposure from medical imaging: Time to regulate? *JAMA*, 304(2), 208-209; Brenner, D.J. (2010). Slowing the increase in the population dose resulting from CT scans. *Radiation Research*, 174(6), 809-815; FDA. (2013). Computed Tomography (CT). Retrieved from http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115317.htm.

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[108] FDA, *supra* note 105.

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[181] Beach, D., Swischuk, J.L., and H.B. Smouse. (2006). Using midlevel providers in interventional radiology. *Seminars in Interventional Radiology*, 23(4), 332; Kole, J., and A. Fiester, *supra* note 12.

[182] Kole, J., and A. Fiester, *supra* note 12.

[183] It might be difficult in practice, however, to shield patients from seeing information in their electronic medical records. Accessing records online, or even through a mobile application, gives patients immediate access to several data components including information regarding medication administration, physical assessment, past medical history, lifestyle, diagnoses, and procedures. Freudenheim, M. (2012, October 8). The ups and downs of electronic medical records. *New York Times*. Retrieved from http://www.nytimes.com/2012/10/09/health/the-ups-and-downs-of-electronic-medical-records-the-digital-doctor.html?pagewanted=all&_r=0; Hayrinen, K., Saranto, K., and P. Nykanen. (2008). Definition, structure, content, use and impacts of electronic health records: A review of the research literature. *International Journal of Medical Informatics*, 77(5), 291-304. To the extent possible, while designing such patient access portals, clinics should attempt to protect patients who opt out of such information. Patients who do not wish to receive all of the medical information also bear some responsibility to avoid such situations where concealing this information might be impossible.

[184] Moore, R.A., et al., *supra* note 13, at 2.

[185] Studies show that people tend to overestimate the risk of rare events by 100-fold and underestimate the risk of common events by a factor of 10. Moore, R.A., et al., *supra* note 13.

[186] Nelson, W., et al., *supra* note 14.

[187] CMS, *supra* note 15.

[188] The Lewin Group. (2005, July). *The Value of Diagnostics Innovation, Adoption and Diffusion into Health*. Retrieved from http://www.lewin.com/~/media/Lewin/Site_Sections/Publications/ValueofDiagnostics.pdf.

[189] CDC, *supra* note 16.

[190] Pickhardt, P.J., et al., *supra* note 116, at 158; Scherer, R., Knudsen, A., and S.D. Pearson. (2008). CT colonography for colorectal cancer screening. *Institute for Clinical and Economic Review*, p. 6. Retrieved from http://www.icer-review.org/index.php/CT-Colonography/View-category.html?dir=ASC&limit=5&order=date.

[191] Volk, M.I., and P.A. Ubel, *supra* note 91.

[192] Hernandez, J.S., *supra* note 17.

[193] Ibid; Ramsey, S.D., et al., *supra* note 17.

[194] The ethical use of cost effectiveness assessments is important for health policy makers to consider. From one perspective, such information can help inform the most efficient use of limited health resources, thereby maximizing health outcomes for the larger population. From another perspective, efficiency is only one value among many that can inform the development of ethically sound health policy. For an overview, see Brock, D. (2004). Ethical Issues in the Use of Cost Effectiveness Analysis for the Prioritization of Health Resources. In G. Khushf, (Ed.). *Handbook of Bioethics: Taking Stock of the Field from a Philosophical Perspective* (pp. 353-380). Dordrecht: Kluwer Academic Publishers.

[195] Those who possess it have the "deliberative capacity to reason well with respect to the means to be used to attain the good of the activity in which we have been engaged." Pellegrino, E.D., and D.C. Thomasma, *supra* note 18, at 90.

[196] Aristotle, *supra* note 19, at 124.

[197] Pellegrino, E.D., and D.C. Thomasma, *supra* note 18, at 87.

[198] An application of Polanyi's theory of "tacit knowledge" to Pellegrino's clinical prudence suggests that much of medical decision making is tacit. Tacit knowledge involves the use of intuition, but this is distinct from purely subjective intuition, or in ethical contexts what might be more commonly considered following one's personal moral conscience. Rather, the "personal knowledge" of professional judgment draws from the individual experiences that help professionals to inform their ability to detect and solve problems. See Henry, S.G. (2006). Recognizing tacit knowledge in medical epistemology. *Theoretical Medicine and Bioethics*, 27(3), 187-213.

[199] See, e.g., American Association of Clinical Endocrinologists (AACE). (n.d.). AACE Guidelines: Disclaimer [Webpage]. Retrieved from https://www.aace.com/publications/guidelines; American Thyroid Association. (n.d.). American Thyroid Association Professional Guidelines [Webpage]. Retrieved from http://thyroidguidelines.net/.

[200] Chandra, A., and J.S. Skinner. (2012). Technology growth and expenditure growth in health care. *Journal of Economic Literature*, 50(3), 645-680; Hellinger, F.J. (1996). The impact of financial incentives on physician behavior in managed care plans: A review of the evidence. *Medical Care Research and Review*, 53(3), 294-314.

[201] Levin, D.C., et al. (2008). Ownership or leasing of MRI facilities by nonradiologist physicians is a rapidly growing trend. *Journal of the American College of Radiology*, 5(2), 105-109; Iglehart, J.K. (2006). The new era of medical imaging—Progress and pitfalls. *New England Journal of Medicine*, 354(26), 2822-2828; Coyle, S.L. (2002). Physician–industry relations. Part 1: Individual physicians. *Annals of Internal Medicine*, 136(5), 396-402.

[202] Coyle, S.L., *supra* note 201.

[203] For example, imaging scans might require analyzing the entire field captured by the scan, not selectively focusing on the organ of immediate concern and deliberately ignoring the rest. Budoff, M.J., Fischer, H., and A. Gopal. (2006). Incidental findings with cardiac CT evaluation: Should we read beyond the heart? *Catheterization and Cardiovascular Interventions*, 68(6), 971.

[204] Agency for Healthcare Research and Quality, *supra* note 21.

[205] CDC, *supra* note 110.

[206] Humphrey, L., et al., *supra* note 141.

[207] U.S. Preventive Services Task Force, *supra* note 141; U.S. Preventive Services Task Force. (2013). *Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation Statement, Evidence Synthesis Number 105*. (AHRQ Publication No. 13-05196-EF-1). Rockville, MD. Retrieved from http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanes105.pdf.

[208] Berland, L.L., *supra* note 116.

[209] CMS, *supra* note 15.

[210] Miller, F.G., Mello, M.M., and S. Joffe. (2008). Incidental findings in human subjects research: What do investigators owe research participants? *Journal of Law, Medicine & Ethics*, 36(2), 277; Richardson, H.S., and M. Cho. (2012). Secondary researchers' duties to return incidental findings and individual research results: A partial entrustment account. *Genetics in Medicine*, 14(4), 467-472; Richardson, H.S., *supra* note 22, at Chapter 6.

[211] For a discussion of depth and duration see Richardson, H.S., and L. Belsky, *supra* note 161; Richardson, H.S., *supra* note 22, at 161-163; and Wolf, S.M., et al., *supra* note 3; For a discussion of degrees of separation between researchers and subjects see Ravitsky, V., and B.S. Wilfond. (2006). Disclosing individual genetic results to research participants. *American Journal of Bioethics*, 6(6), 8-17.

[212] Kirschen, M.P., Jaworska, A., and J. Illes. (2006). Subjects' expectations in neuroimaging research. *Magnetic Resonance Imaging*, 23(2), 205-209.

[213] Miller, F.G., and H. Brody. (2002). What makes placebo-controlled trials unethical? *American Journal of Bioethics*, 2(2), 3-9; Parker, L.S. (2006). Best laid plans for offering results go awry. *American Journal of Bioethics*, 6(6), 22-23; Sharp, H.M., and R.D. Orr. (2010). When "minimal risk" research yields clinically-significant data, maybe the risks aren't so minimal. *American Journal of Bioethics*, 4(2), 33.

[214] The Royal College of Radiologists. (2010). *Management of Incidental Findings Detected During Research*. London: The Royal College of Radiologists. Retrieved from https://www.rcr.ac.uk/docs/radiology/pdf/BFCR(11)8_Ethics.pdf.

[215] Kirschen, M.P., Jaworska, A., and J. Illes, *supra* note 212.

[216] Caulfield, T., et al., (2008). Research ethics recommendations for whole-genome research: Consensus statement. *PLoS Biology*, 6(3), 430-434; Cho, M. (2008). Understanding Incidental Findings in the Context of Genetics and Genomics. *Journal of Law, Medicine & Ethics*, 36(2), 280-285; Fabsitz, R.R., et al. (2010). Ethical and practical guidelines for reporting genetic research results to study participants: Updated guidelines from a National Heart, Lung and Blood Institute working group. *Circulation: Cardiovascular Genetics*, 3(6), 574-580; Ravitsky, V., and B.S. Wilfond, *supra* note 211.

[217] Kohane, I.S., and P.L. Taylor. (2010). Multidimensional results reporting to participants in genomic studies: Getting it right. *Science Translational Medicine*, 2(37), 1-4.

[218] Caulfield, T., et al., *supra* note 216; Fabsitz, R.R., et al., *supra* note 216; Kohane, I.S., and P.L. Taylor, *supra* note 217.

[219] Fabsitz, R.R., et al., *supra* note 216.

[220] Bombard, Y., Offit, L., and M.E. Robson. (2012). Risks to relatives in genomic research: A duty to warn. *American Journal of Bioethics*, 12(10), 12-14; Keane, M.A. (2008). Incidental findings in human subjects research: From imaging to genomics – Institutional review board approaches to the incidental findings problem. *Journal of Law, Medicine & Ethics*, 36(2), 352-355; Schmidt, C.O., et al., *supra* note 116.

[221] Bombard, Y., Offit, L., and M.E. Robson, *supra* note 220; Keane, M.A., *supra* note 220.

[222] Fernandez, C.V., Kodish, E., and C. Weijer. (2003). Informing study participants of research results: An ethical imperative. *IRB*, 25(3), 12-19; Illes, J., and V.N. Chin, *supra* note 101, at 298-312; Illes, J., et al., *supra* note 49, at 783-784; Terry, S.F. (2012).The tension between policy and practice in returning research results and incidental findings in genomic biobank research. *Minnesota Journal of Law, Science & Technology*, 13, 691.

[223] The Clinical Laboratory Improvement Amendments (CLIA) was passed in 1988 as a means of establishing standards of accuracy and reliability of all laboratory results intended for clinical use. Laboratory Requirements, 53 Fed. Reg. 29590 (Aug. 5, 1988).

[224] See, e.g., Wolf, S.M. (2012). The role of law in the debate over return of research results and incidental findings: The challenge of developing law for translational science. *Minnesota Journal of Law, Science & Technology*, 13(2), 435-448.

[225] Wolf, S., Paradise, J.D., and C. Caga-anan. (2008). The law of incidental findings in human subjects research: Establishing researchers' duties. *Journal of Law, Medicine & Ethics*, 36(2), 361-383; Wolf, S.M. et al., *supra* note 3.

[226] *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.116 (b)(5).

[227] Health Insurance Portability and Accountability Act (HIPAA), 110 Stat. 1936 (1996).

[228] Ibid.

[229] Gordon, M.P., *supra* note 34, at 225-260. In 2011, CMS and the U.S. Department of Health and Human Services Office for Civil Rights proposed a rule that would modify HIPAA to require clinical labs to directly report laboratory test results to patients upon request. This proposed rule is unlikely to apply to research participants as the rule is limited to patients, though it is possible that either in its final form or as implemented CMS could enlarge the rule to include individuals who are research participants. The rule is also limited to CLIA-certified laboratories and would not apply to research laboratories that are not CLIA-certified. CLIA Program and HIPAA Privacy Rule; Patients Access to Test Reports, 76 Fed. Reg. 56, 712-56, 724. (Sept. 14, 2011).

[230] CLIA, 57 Fed Reg. 7139, 493.3 (b)(2) (Feb. 28, 1992); Fabsitz, R.R., et al., *supra* note 216.

[231] Fabsitz, R.R., et al., *supra* note 216.

[232] National Research Council and Institute of Medicine Committee on Guidelines for Human Embryonic Stem Cell Research. (2005). *Guidelines for Human Embryonic Stem Cell Research*. Washington, DC: National Academies Press; Wolf, S.M., et al., *supra* note 3.

[233] Pike, E.R., Rothenberg, K., and B.E. Berkman. (2013). Finding fault?: Exploring legal duties to return incidental findings in genomic research. *Georgetown Law Journal* [forthcoming]; Zarzeczny, A., and T. Caulfield. (2012). Legal liability and research ethics boards: The case of neuroimaging and incidental findings. *International Journal of Law and Psychiatry*, 35(2), 137-145.

[234] See, e.g., Knoppers, B.M., and R. Chadwick. (2005). Human genetic research: Emerging trends in ethics. *Nature Reviews Genetics*, 6(1), 75-79; Kristman, V.I., and N. Krieger. (2008). Information disclosure in population-based research involving genetics: A framework for the practice of ethics in epidemiology. *Annals of Epidemiology*, 18(4), 335-341; Ravitsky, V., and B.S. Wilfond, *supra* note 211. For a discussion of traditional research ethics principles see The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *supra* note 64; and PCSBI, *supra* note 70.

[235] PCSBI, *supra* note 70.

[236] Richardson, H.S., *supra* note 22.

[237] Ravitsky, V., and B.S. Wilfond, *supra* note 211.

[238] Rothstein, M.A. (2013). Should researchers disclose results to descendants. *American Journal of Bioethics*, 13(10), 64-65.

[239] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *supra* note 64 ("The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.").

[240] Miller, F.G., Mello, M.M., and S. Joffe. (2008). Incidental findings in human subjects research: What do investigators owe research participants? *Journal of Law, Medicine & Ethics*, 36(2), 276; Richardson, H.S., *supra* note 22, at Chapter 3.

[241] Richardson, H.S., *supra* note 22, at Chapter 3.

[242] Black, W.C., and H.G. Welch. (1993). Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *New England Journal of Medicine*, 328(17), 1237-1243.

[243] For a discussion of harm related to return of findings see Miller, F.G., Mello, M.M., and S. Joffe, *supra* note 210, at 271-279; Meacham, M.C., et al. (2010). Researcher perspectives on disclosure of incidental findings in genetic research. *Journal of Empirical Research*, 5(3), 31-41; For a contrasting view see Biesecker, L., Chief and Senior Investigator, Genetic Disease Research Branch, National Human Genome Research Institute. (2013, May 14). Comments submitted to PCSBI.

[244] Berg, J.S., et al. (2013). An informatics approach to analyzing the incidentalome. *Genetics in Medicine*, 15(1), 36-44; Rangel, E.K. (2010). Management of incidental findings in neuro-imaging research: Framework and recommendations. *Journal of Law, Medicine & Ethics*, 38(1), 117-126.

[245] Rangel, E.K., *supra* note 244.

[246] Wolf, S.M., et al., *supra* note 3.

[247] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *supra* note 64; PCSBI, *supra* note 70, at 6.

[248] PCSBI, *supra* note 70, at 24-25.

[249] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *supra* note 64.

[250] National Cancer Institute. (2003). *Area Socioeconomic Variations in U.S. Cancer Incidence, Mortality, Stage, Treatment, and Survival, 1975-1999. NCI Cancer Surveillance Monograph Series, Number 4*. (NIH Publication No. 03-0000). Bethesda, MD: National Cancer Institute. Retrieved from http://open-dev.umms.med.umich.edu/sites/default/files/1232/reading-resources-1/Singh-fullarticle.pdf.

[251] PCSBI, *supra* note 70, at 141-142.

[252] Ibid, at 27-28, 141-145.

[253] Ibid.

[254] Ibid.

[255] Ibid, at 28, 141.

[256] Richardson, H.S., *supra* note 22; Knoppers, B.M., et al., *supra* note 22.

[257] *Protection of Human Subjects, HHS*, *supra* note 23.

[258] Fabsitz, R.R., et al., *supra* note 216.

[259] Drazin, D., et al., *supra* note 129.

[260] Some health insurers now require that genetic counseling accompany testing for genetic predispositions to diseases like breast cancer. Genetic counseling helps patients (and research participants) better understand and interpret the nature of genetic findings, and can alleviate fears and anxieties about the results. See, e.g., Langreth, R. (2013, August 19) Cigna demands counseling for breast test in myriad threats. *Bloomberg*. Retrieved from http://mobile.bloomberg.com/news/2013-08-19/cigna-demands-counseling-for-breast-test-in-myriad-threat.html?source=email_rt_mc_body.

[261] Green, R.C., Associate Director for Research, Partners HealthCare Center for Personalized Genetic Medicine, Associate Professor of Medicine, Division of Genetics, Brigham and Women's Hospital and Harvard Medical School. (2013). Presentation to PCSBI, April 30. Retrieved from http://bioethics.gov/node/1616.

[262] The availability of DTC biological specimens testing and imaging has grown over the last decade. DTC genetic testing has also increased over this period, though there has been a contraction in the DTC genetic services market during the last several years. Mathews, A.W. (2011, January 11). Worried about cholesterol? Order your own tests. *Wall Street Journal*. Retrieved from http://online.wsj.com/article/SB10001424052748704458204576073913850150324.html (Stating that DTC lab tests are "a small but growing part of the overall lab industry" and estimating that people are "spending about $20 million a year for such tests, and the segment [i]s growing at 15% to 20% annually."); Wallace, E.A., Schumann, J.H., and S.E. Weinberger. (2012). Ethics of commercial screening tests. *Annals of Internal Medicine*, 157(10), 747-748 (discussing the growth of DTC imaging services); Su, Y., Howard, H.C., and P. Borry. (2011). Users' motivations to purchase direct-to-consumer genome-wide testing: An exploratory study of personal stories. *Journal of Community Genetics*, 2(3), 135-146 (Stating that the DTC genetic testing market has rapidly expanded); Allison, M. (2012). Direct-to-consumer genomics reinvents itself. *Nature Biotechnology*, 30(11), 1027-1029 (explaining that "DTC genomics has changed dramatically over the past few years…some companies—those with actual products—have turned from working directly with consumers to offering their tests only through physicians, in part because of FDA pressure, but also because consumer demand appears to be lackluster.").

[263] The discovery and return of incidental findings in the DTC context takes place within the larger domain of general DTC business practices. For this reason, a thorough consideration of incidental findings in the DTC context must take into account the ethically relevant aspects of these general practices. A complete analysis of the ethics of such larger phenomena as the commercialization of health care in the United States, skyrocketing costs for both consumers and government, and issues of access to clinical care are beyond the scope of this report. This analysis addresses these larger factors only to the extent that they clarify what must be done to anticipate and respond to consumers' sensitive information.

[264] See, e.g., FDA. (n.d.). First Rapid Home-Use HIV Kit Approved for Self-Testing [Webpage]. Retrieved from http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm310545.htm; and Office on Women's Health. (n.d.). Pregnancy tests fact sheet [Webpage]. Retrieved from http://womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-tests.cfm.

[265] Mathews, A.W., *supra* note 262.

[266] DirectLabs explains on its website "[w]e respect your privacy and maintain confidentiality. You are the only one who receives the results unless you specify otherwise, with a signed HIPAA release. Not even your insurance company will obtain results from DLS [DirectLabs] and/or its associates without written consent from you." DirectLabs. (2013). Frequently Asked Questions [Webpage]. Retrieved from https://www.directlabs.com/AboutUs/FAQ/tabid/65/language/en-US/Default.aspx.

[267] Su, Y., Howard, H.C., and P. Borry, *supra* note 262.

[268] Mountain, J., *supra* note 54.

[269] Hogarth, S., Javitt, G., and D. Melzer. (2008). The current landscape for direct-to-consumer genetic testing: Legal, ethical, and policy issues. *Annual Review of Genomics Human Genetics*, 9, 161-182.

[270] For example, Connecticut has banned DTC fetal ultrasounds. Maine allows for testing without a physician's referral for glucose, colon cancer, pregnancy, and cholesterol tests, but prohibits other tests. Genetics and Public Policy Center. (2007). Publication Announcement: Comparison of State Laws for Direct-to-Consumer Testing [Press release]. Retrieved from http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=81.

[271] Genetics and Public Policy Center. (2007). Survey of Direct-to-Consumer Testing Statues and Regulations. Retrieved from http://www.dnapolicy.org/resources/DTCStateLawChart.pdf; Schlanger, S. (2011). Filling in the cracks: Improving the regulation of direct-to-consumer genetic tests. *Journal of Health Care Law and Policy*, 14, Supp. 11, S1-S29.

[272] Schlanger, S., *supra* note 271.

[273] In addition to being regulated for safety by FDA as medical devices, imaging products, including CT, MRI, and ultrasonography products, are also regulated for safety by FDA as radiation-emitting electronic products. FDA. (2010). Does the Product Emit Radiation? [Webpage]. Retrieved from http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051504.htm; FDA. (2010). Full-Body CT Scans—What You Need to Know. [Webpage]. Retrieved from http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115340.htm.

[274] FDA, *supra* note 273.

[275] See, e.g., Warning letter from Alberto Gutierrez to Ann Wojcicki. (2013, November 22). Retrieved from http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm; Although as DTC genetic testing companies move away from providing sequencing interpretation and corresponding health care information to providing either sequencing data or medical information, FDA will face new challenges to regulation. Spector-Bagdady, K. and E.R. Pike (Forthcoming, 2014). Consuming Genomics: Regulating Direct-to-Consumer Genomic Interpretation. *Nebraska Law Review*.

[276] CMS. (2013). Clinical Laboratory Improvement Amendments (CLIA) [Webpage]. Retrieved from http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/.

[277] *Federal Trade Commission, Promotion of Export Trade and Prevention of Unfair Methods of Competition*, 15 U.S.C. §§ 41-58.

[278] Letter from Michael Perschuck, et al., Chairman, Federal Trade Commission, to Wendell H. Ford, Chairman, Consumer Subcommittee, and John C. Danforth, Ranking Minority Member, Consumer Subcommittee, Committee on Commerce, Science, and Transportation. (1980, December 17). FTC Policy Statement on Unfairness. Retrieved from http://www.ftc.gov/bcp/policystmt/ad-unfair.htm.

[279] Letter from James C. Miller III, Chairman, Federal Trade Commission, to John D. Dingell, Chairman, Committee on Energy and Commerce. (1983, October 14). FTC Policy Statement on Deception. Retrieved from http://www.ftc.gov/bcp/policystmt/ad-decept.htm.

[280] A contract is a promise that the law will enforce, or the performance of which will, in some way, be recognized as a legal duty. John Edward Murray, Murray on Contracts Chapter 1 §2 (5th ed. 2011). See also E. Allan Farnsworth, Contracts §1.1 4 (4th ed. 2004).

[281] Some commentators have questioned courts that narrowly rely on the terms and conditions provided by an online company without taking into account other information and representations made elsewhere on the website. See Hartzog, W. (2011). Website design as contract. *American University Law Review*, 60, 1635-1671.

[282] Ossorio, P.N. (2001). Product liability for predictive genetic tests. *Jurimetrics Journal*, 41, 239-260.

[283] Ibid.

[284] Smith, A. (1976). *An Inquiry into the Nature and Causes of the Wealth of Nations*. R.H. Campbell, A.S. Skinner, and W.B. Todd. (Eds). Oxford: Oxford University Press.

[285] Ibid; Stigler, G.J. (1957). Perfect competition, historically contemplated. *Journal of Political Economy*, 65(1), 1-17.

[286] MacIntyre, A., *supra* note 68; Richardson, H.S., *supra* note 22, at 75-76; Scanlon, T.S., *supra* note 68.

[287] American Medical Association. (2005). Report of the Council on Ethical and Judicial Affairs: Direct-to-Consumer Diagnostic Imaging Tests. Retrieved from http://www.ama-assn.org/resources/doc/code-medical-ethics/8045a.pdf.

[288] This argument for the professional duties of DTC providers is based on Henry Richardson's analogous arguments regarding researchers. Richardson, H.S., *supra* note 22, at 59-98.

[289] PCSBI, *supra* note 70, at 16-18.

[290] Ibid, at 28, 141.

[291] Ibid, at 141.

[292] Ibid, at 5.

[293] 23andMe. (2012, September 7). Customer Care: What health conditions are not covered by 23andMe's Personal Genome Service? [Webpage]. Retrieved from https://customercare.23andme.com/entries/21979637-What-health-conditions-are-not-covered-by-23andMe-s-Personal-Genome-Service-.

[294] CPSC, *supra* note 24; NHTSA, *supra* note 24; FCC, *supra* note 24.

[295] Carson, T.L., *supra* note 25.

[296] Ibid.

[297] Donaldson, T., *supra* note 27.

[298] Pharmaceutical Research and Manufacturers of America (PhRMA). (n.d.). Ethical relationships with health care professionals are critical to our mission [Webpage]. Retrieved from http://www.phrma.org/code-on-interactions-with-healthcare-professionals; PhRMA. (2009). 105 CMR970.000: Pharmaceutical and Medical Device Manufacturer Conduct. Retrieved from http://policymed.typepad.com/files/mass-code-of-conduct----final-3-11-09.pdf; See, e.g., Cal. Health & Safety §§ 119400-119402 (Deering 2005).

[299] American Medical Association, *supra* note 287.

[300] American Institute of Ultrasound in Medicine. (2012). Keepsake Fetal Imaging. Retrieved from http://www.aium.org/officialStatements/31.

[301] Mountain, J., *supra* note 54.

[302] Inherent Health. (2009). Frequently Asked Questions [Webpage]. Retrieved from http://www.inherenthealth.com/faq.aspx#S5Q2.

APPENDICES

Appendix I: Past National Recommendations Regarding Incidental and Secondary Findings

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	**CONTEXT; MODALITY**	**KEY POINTS**
American College of Medical Genetics and Genomics (ACMG), ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing (2013)*	Clinical; Large-Scale Genetic Sequencing	When large-scale genetic sequencing is conducted in the clinic, "a minimum list of conditions, genes and variants should be routinely evaluated and reported to the ordering clinician who can place them into the context of that patient's medical and family history, physical examination and other laboratory testing." Only known variants of tested genes should be reported. Any findings arising from such evaluation should be reported by laboratories "without seeking preferences from the patient and family and without limitation due to the patient's age." A clinician "should be properly trained and prepared in genetics and genomics with an understanding of genetic counseling, pedigree analysis and risk assessment to provide pre-test and post-test patient care associated with clinical sequencing." "It is the responsibility of the ordering clinician/team to provide comprehensive pre- and post-test counseling for the patient."
Public Population Project in Genomics and Society, Population Studies: Return of Research Results and Incidental Findings Policy Statement (2013)†	Research (Biobank); Large-Scale Genetic Sequencing	Disclosure of individual research results and incidental findings to subjects should be considered when: • "the participant has consented thereto in the initial consent form or at a later time; • the findings are analytically valid (i.e., confirmed independently); • they reveal a significant risk of a serious health condition; and • they are actionable." Disclosure of individual research results and incidental findings to subjects might be considered when: • "the participant has consented thereto in the initial consent form or at a later time; • the findings are analytically valid (i.e., confirmed independently); • they reveal an established risk of likely health importance to the participant; and • they have a likely therapeutic benefit."
National Human Genome Research Institute, Federal Policy Recommendations Including [the Health Insurance Portability and Accountability Act (HIPAA)] (2012)‡	Research; Large-Scale Genetic Sequencing	Individual research results should be available to participants except when: • "[t]he information includes information obtained under a promise of confidentiality, is about another person, and patient inspection would cause harm to another individual…" • [a]ccess would break the 'masking' of the study or otherwise significantly interfere with the conduct or results of the study; or • [t]he research results are of unproven clinical validity, and the IRB has judged that there is no benefit to the research subjects." In this latter case, "the informed consent must explicitly state that individual research results will not be shared."

* Green, R.C., et al. (2013). ACMG recommendations for reporting of incidental findings in clinical exams and genome sequencing. *Genetics in Medicine*, 15(4), 565-574; American College of Medical Genetics and Genomics. (2013). Incidental Findings in Clinical Genomics: A Clarification—A Policy Statement of the American College of Medical Genetics and Genomics, Bethesda, MD. Retrieved from https://www.acmg.net/docs/Incidental_Findings_in_Clinical_genomics_A_Clarification.pdf.

† Knoppers, B.M., et al. (2013). Population studies: Return of research results and incidental findings Policy Statement. *European Journal of Human Genetics*, 21(3), 245-247 (formatting changed for Appendix presentation).

‡ National Human Genome Research Institute. (2012, February 28). Federal Policy Recommendations Including HIPAA. Retrieved from http://www.genome.gov/11510216.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
Wolf, Susan, et al., Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Datasets (2012)*	Research; Large-Scale Genetic Sequencing	Biobanks should strive to: • Fulfill their responsibilities with respect to incidental findings. • Develop explicit policy on whether incidental findings and individual research results should be returned by: » "[c]larifying the criteria for evaluating findings and the roster of returnable [incidental findings] and [individual research results];" » "[a]nalyzing a particular finding to decide whether it should be offered to the contributor;" » re-identifying that contributor; and » re-contacting the contributor to offer the finding. • "[A]nalyze whether a particular finding qualifies as an [incidental finding] or [individual research result] that should be offered to a consenting contributor or contributors." • Anticipate how they will handle identification, re-identification, and re-contacting of contributors. Researchers in the biobank research system should offer to return incidental findings and individual research results that meet all of the following criteria: • "[t]he findings are analytically valid; • [r]eturning them to the contributor comports with applicable law, including [the Clinical Laboratory Improvement Amendments] (CLIA) (which may require ascertaining or verifying results in a CLIA-certified lab); • [t]he contributor has been offered the option of consenting to return of individual findings (either in the initial informed consent process, or in a subsequent consent process that may be a request for an individual's consent or part of a larger effort to elicit many contributors' consent) and has opted to receive them; • [t]he findings reveal an established and substantial risk of a serious health condition; and • the findings are clinically actionable." Researchers in the biobank research system might offer to return incidental findings and individual research results that fail to meet the above criteria, if they instead meet all of the following criteria: • "[t]he findings are analytically valid; • [r]eturning them to the contributor comports with applicable law, including CLIA…; • [t]he contributor has been offered the option of consenting to return of individual findings (either in the initial informed consent process or subsequently…) and has opted to receive them; and • [t]he findings reveal an established and substantial risk of likely health or reproductive importance or personal utility to the contributor and return is likely to provide net benefit from the contributor's perspective."

* Wolf, S.M., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived datasets. *Genetics in Medicine*, 14(4), 361-384.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
Freda, Pamela, et al., Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline (2011)*	Clinical; Imaging	Patients with an incidentally found pituitary incidentaloma should undergo a history and physical examination, laboratory evaluations screening for hormone hypersecretion and for hypopituitarism, and a visual field examination if the lesion touches the optic nerve or chiasm. Patients with pituitary incidentalomas that do not meet the criteria for surgical removal should have follow up including clinical assessments, neuroimaging, visual field examinations for incidentalomas that touch the optic nerve or chiasm, and endocrine testing for macroincidentalomas. Patients should be referred to surgery if they have a visual field deficit due to the lesion, signs of compression by the tumor, a lesion touching the optic nerves or chiasm, pituitary apoplexy with visual disturbance, or a hypersecreting tumor that is not a prolactinoma.
American College of Radiology (ACR), Managing Incidental Findings on Abdominal [computed tomography (CT)]: White Paper of the ACR Incidental Findings Committee (2010)†	Clinical; Imaging	Incidental findings on abdominal CT scans should be evaluated and addressed based on certain criteria of the mass and the organ in which the mass was found. In the kidneys, cystic renal masses should be ignored or observed if they are less than or equal to 3 cm or if there is no measurable enhancement, and should be operated on if they have thickened irregular or smooth walls or septa, with measurable enhancement. Solid renal masses should be operated on if they are larger than 1 cm and should be observed if they are smaller than 1 cm.
National Heart, Lung, and Blood Institute (NHLBI), NHLBI Working Group on Reporting Genetic Results in Research Studies, Meeting Summary (2010)‡	Research; Large-Scale Genetic Sequencing	Disclosure of individual research result to subjects *should* occur if/when the following are satisfied: • "[t]he genetic finding has important health implications for the participant, and the associated risks are established and substantial; • the genetic finding is actionable; that is, there are established therapeutic or preventive interventions or other available actions that have the potential to change the clinical course of the disease; • the test is analytically valid and the disclosure plan complies with all applicable laws; and • during the informed consent process or subsequently, the study participant has opted to receive his or her individual genetic results." Disclosure of individual research result to subjects may occur if/when the following are satisfied: • "[t]he investigator has concluded that the potential benefits of disclosure outweigh the risks from the participant's perspective; • [t]he investigator's [institutional review board (IRB)] has approved the disclosure plan; • [t]he test is analytically valid and the disclosure plan complies with all applicable laws; and • [d]uring the informed consent process or subsequently, the study participant has opted to receive his/her individual genetic results."

* Freda, P.U., et al. (2011). Pituitary incidentaloma: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, 96(4), 894-904.

† Berland, L.L., et al. (2010). Managing incidental findings on abdominal CT: White paper of the ACR Incidental Findings Committee. *Journal of the American College of Radiology*, 7(10), 754-773.

‡ Fabsitz, R.R., et al. (2010). Ethical and practical guidelines for reporting genetic research results to study participants: Updated guidelines from a National Heart, Lung and Blood Institute working group. *Circulation: Cardiovascular Genetics*, 3(6), 574-580 (formatting changed for Appendix presentation) (updating an earlier set of NHLBI working group recommendations: Brookman, E.B., et al. (2006). Reporting genetic results in research studies: Summary and recommendations of an NHLBI working group. *American Journal of Medical Genetics Part A*, 140, 1033-1040.).

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
Wolf, Susan, et al., Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations (2008)*	Research; Large-Scale Genetic Sequencing	Researchers have an obligation to: • plan for the types of incidental findings potentially produced and "consider how quickly members of the research team should bring a suspected [incidental finding] to the attention of the principal investigator and how quickly the principal investigator should act to evaluate the [incidental finding];" • address incidental findings with research participants during the informed consent process; • "[p]lan to verify and evaluate a suspected [incidental finding], with an expert consultant if needed;" • "[p]lan to determine whether to report [incidental findings] based on likely health or reproductive importance;" and • in some cases offer to disclose incidental findings directly to research participants. Disclosure of incidental findings should be based on the net benefit of disclosure: • *Strong net benefit*: incidental finding reveals a "condition likely to be life-threatening or a condition likely to be grave that can be avoided or ameliorated." Researchers should offer to disclose. • *Possible net benefit*: incidental finding might offer more benefit than burden to participant; reveals health condition that participant is likely to view as important. Researchers may disclose, but are not obligated to do so. • *Unlikely net benefit*: incidental finding offers more burden than benefit. Researcher should not disclose.
Illes, Judy, et al., Practical Approaches to Incidental Findings in Brain Imaging Research (2008)†	Research; Imaging	Researchers should: • "[e]stablish a pathway for managing incidental findings that is fully transparent and addressed in the institutional review board review and consent process, including explicit language about how incidental findings will be handled, subject selection, and responsibility for follow up;" • "[a]llow for…the involvement of a medical professional who is competent and readily available to interpret neuroimaging scans for clinically significant information;" • "[d]isclose incidental findings to a subject or surrogate first" (communication is the responsibility of the principal investigator or a qualified member of the research team, if the principal investigator is not a physician); and • "[c]ommunicate the news of an incidental finding verbally and in a timely manner…and follow up with written communication that draws on the informed consent language."
Caulfield, Timothy, et al., Research Ethics Recommendations for Whole-Genome Research: Consensus Statement (2008)‡	Research; Large-Scale Genetic Sequencing	Research involving genome sequencing should have a process for determining whether findings, including incidental findings, meet the requirements for the return to the participant. This process should be approved by a research ethics review entity. Research participants should be informed of this process during consent. The consent process should also acknowledge the participants' right not to know certain results.

* Wolf, S.M., et al. (2008). Managing incidental findings in human subjects research: Analysis and recommendations. *Journal of Law, Medicine & Ethics*, 36(2), 220-248.

† Illes, J., et al. (2008). Practical approaches to incidental findings in brain imaging research. *Neurology*, 70(5), 384-390.

‡ Caulfield, T., et al. (2008). Research ethics recommendations for whole-genome research: Consensus statement. *PLoS Biology*, 6(3), 430-435.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	**CONTEXT; MODALITY**	**KEY POINTS**
National Research Council and Institute of Medicine, Guidelines for Human Embryonic Stem Cell Research (2005)*	Research; Biological Specimens	Obligations to report individual research results to participants during embryonic stem cell research should depend on: • The reliability of the findings; and • The significance of the findings to the participants' health and wellbeing. Research results should not be returned if tests were not conducted in CLIA-approved lab.
National Institute of Neurological Disorders and Stroke, Detection and Disclosure of Incidental Findings in Neuroimaging Research (2005)†	Research; Imaging	The potential for incidental findings should be anticipated in experimental design. Researchers, scientists, and clinicians should develop a plan to handle the discovery of an incidental finding. This process should include review of the neuroimaging scan by a competent professional. Communication of the incidental finding to the research subject or surrogate should be done by the principal investigator or another qualified member of the research team. Communication of the incidental finding should be done verbally, in a timely manner, and documented in writing. Incidental findings should be included in the informed consent process, including information about follow up and cost of managing the finding. The process for managing an incidental finding must be completely transparent, and template disclosure language should be provided to the IRB. The process for managing incidental findings should not impede neuroimaging research, but should "highlight the responsibility of the research team." A database of incidental findings "would be a valuable scientific resource."
Beskow, Laura M., et al. (U.S. Centers for Disease Control and Prevention), Informed Consent for Population-Based Research Involving Genetics (2001)‡	Research; Large-Scale Genetic Sequencing	"When the risks identified in the study are both valid and associated with a proven intervention for risk reduction, disclosure may be appropriate."

* National Research Council and Institute of Medicine of the National Academies. (2005). *Guidelines for Human Embryonic Stem Cell Research*. Washington, D.C.: The National Academies Press.

† National Institutes of Health. (2005). Detection and Disclosure of Incidental Findings in Neuroimaging Research. Retrieved from http://www.ninds.nih.gov/news_and_events/proceedings/ifexecsummary.htm.

‡ Beskow, L.M., et al. (2001). Informed consent for population-based research involving genetics. *JAMA*, 286(18), 2315-2321.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
Medical Research Council, Human Tissue and Biological Samples for Use in Research – Operational and Ethical guidelines (2001)*	Research; Biological Specimens	When an incidental finding has "immediate clinical relevance, the clinician involved has a duty of care to inform the research participant, either directly or via the clinician responsible for his or her care. The clinician responsible for care should always be notified." Research participants should be informed of these practices during consent.
National Bioethics Advisory Commission, Research Involving Human Biological Materials: Ethical Issues and Policy Guidance (1999)†	Research; Large-Scale Genetic Sequencing and Biological Specimens	Disclosure of individual research result to participants should only occur if/when: • "the findings are scientifically valid and confirmed, • the findings have significant implications for the subject's health concerns, and • the course of action to ameliorate or treat these concerns is readily available." The "…research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings." "When research results are disclosed to a subject, appropriate medical advice or referral should be provided."
National Human Genome Research Institute, Final Report of the Task Force on Genetic Testing (1997)‡	Direct-to-Consumer; Genetic Testing	Information from genetic tests presented directly to the public must be accurate and include information about the risks and limitations in addition to the benefits. Consumers should discuss testing with a health care provider. Advertising or marketing of predictive genetic tests is discouraged.

* Medical Research Council. (2001, May 4). Human Tissue and Biological Samples for use in Research – Operational and Ethical guidelines. Retrieved from http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002420.

† National Bioethics Advisory Commission (NBAC). (1999). Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Rockville, MD: NBAC. Retrieved from http://bioethics.georgetown.edu/nbac/hbm.pdf (formatting changed for Appendix presentation).

‡ National Human Genome Research Institute. (1997, September). Promoting Safe and Effective Genetic Testing in the United States. Retrieved from http://www.genome.gov/10002403.

Appendix II: Past International Recommendations Regarding Incidental and Secondary Findings

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	**CONTEXT; MODALITY**	**KEY POINTS**
European Society of Human Genetics, Whole-Genome Sequencing in Health Care: Recommendations of the European Society of Human Genetics (2013)*	Clinical; Large-Scale Genetic Sequencing	Targeted approaches are preferable to "avoid unsolicited findings or findings that cannot be interpreted." Filtering should be used to filter out known genetic variants with limited or no clinical utility. Guidelines for informed consent regarding diagnostic testing should be developed. "Patients' claims to a right not to know about findings do not automatically over-ride professional responsibilities…Patient groups could provide important input into how this should be handled." "[G]uidelines need to be established [regarding testing minors] as to what unsolicited information should be disclosed to balance" the interests of the child and parental rights.
Danish Council of Ethics, Genome Testing: Ethical Dilemmas in Relation to Diagnostics, Research and Direct-to-Consumer Testing (2012)†	Clinical, Research, and DTC; Large-Scale Genetic Sequencing	Large-scale genetic testing should be "accompanied by impartial and comprehensive information as well as counseling, both before and after testing," whether conducted in the clinic, research, or DTC setting. Patients should be given a "degree of involvement in deciding whether, and to what extent, they are to receive feedback on any incidental findings." The conversation should take place prior to testing. "Clinical trial subjects should not be offered information about genetic risk factors."
PHG Foundation [UK], Next Steps in the Sequence: The Implications of Whole Genome Sequencing for Health (2011)‡	Clinical; Large-Scale Genetic Sequencing	The possibility of incidental findings should be minimized whenever possible. Targeted tests or analyses that answer specific clinical questions are preferred. Health care professionals are not obligated to provide incidental findings that do not relate to the clinical question, except for cases in which they are unavoidably discovered and have high predictive value. There is no obligation to provide patients with their raw genomic sequence data. Informed consent might not be sufficient to deal with incidental findings. The operationalization of a right not to know about findings is not straightforward. The possibility of identifying clinically actionable findings should be reflected in pre-test and post-test counseling. The debate over opportunistic whole genome sequencing screening has not yet been undertaken. Any decision must consider the relative risks and benefits both to a patient and the wider community. The requirement to "do no harm" might require not subjecting patients to years of invasive screening. Where variants are of unknown significance, the responsibility to investigate might be less clear.

* Van El, C.G., et al. (2013). Whole-genome sequencing in health care: Recommendations of the European Society of Human Genetics. *European Journal of Human Genetics*, 21, 580-584.

† The Danish Council of Ethics. (2012). *Executive Summary. Genome testing: Ethical dilemmas in relation to diagnostics, research and direct-to-consumer testing*. Retrieved from: http://etiskraad.dk/en/Udgivelser/BookPage.aspx?bookID={0F84411D-1DD3-49CD-B8ED-679D29419E20}.

‡ PHG Foundation. (2011). Next steps in the sequence: The implications of whole genome sequencing for health in the UK. Cambridge: PHG Foundation. Retrieved from http://www.phgfoundation.org/file/10363.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
The Royal College of Radiologists [UK], Management of Incidental Findings Detected During Research Imaging (2010)*	Research; Imaging	Imaging research centers should assess the risk of incidental findings that they are likely to encounter. "Researchers must provide a reasonable standard of care. They should aim to give feedback on health information that is likely to result in avoidance or significant harm to participant." Someone "able to judge the potential health implications" of a finding should be available to advise a participant. "Research participants should be fully informed of the likelihood" of incidental findings, the threat that incidental findings might pose, how researchers will identify incidental findings, and the problems of false positives and false negatives. Collaborations should be implemented to im increase access to expert image interpretations. Guidelines should describe when uncertain cases should be escalated to professionals with more expertise. "Information on incidental findings should be provided to the participant and their clinically responsible physician." Results that are unverified should not be returned.
Nuffield Council on Bioethics [UK], Medical Profiling and Online Medicine: The Ethics of "Personalized Healthcare" in a Consumer Age (2010)†	DTC; Large-Scale Genetic Sequencing and Imaging	Genetic testing • A publically funded website should be created that includes: information about DTC genetic services, the potential risks and benefits, difficulties of establishing clinical validity, and the possibility of finding out about conditions with no treatments. • Prior to purchase, DTC companies should make the following information available: » information about the quality, evidence, and limitations of the tests; » that test results might require interpretation by a qualified medical practitioner or genetic counselor; » the possibility of finding serious health problems and family genetic relationships; » the nature of the risk communicated to the consumer (e.g., absolute or relative); » whether third parties have access to the data; » how data are protected; and » where to find independent information about the service. • DTC companies should require that "their customers at the point of sale click on a statement confirming that they have the consent of the person whose DNA they intend to have analyzed." • Companies should only analyze the DNA of children if a genetic test meets the criteria of the UK National Screening Committee, and valid parental consent has been obtained. Imaging • Independent research on the impact and effects on individuals should be conducted. • Services should be appropriately regulated. • Clinical practice should adapt to circumstances in which patients have had these tests.

* The Royal College of Radiologists. (2010). Management of Incidental Findings Detected During Research. London: The Royal College of Radiologists. Retrieved from https://www.rcr.ac.uk/docs/radiology/pdf/BFCR(11)8_Ethics.pdf.

† Nuffield Council on Bioethics. (2010). *Medical Profiling and Online Medicine: The ethics of 'personalized healthcare' in a consumer age*. London: Nuffield Press.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	**CONTEXT; MODALITY**	**KEY POINTS**
Canadian College of Medical Geneticists, Direct-to-Consumer Genetic Testing (2011)*	DTC; Large-Scale Genetic Sequencing	DTC testing should comply with the following standards and regulations: • "[g]enetic testing must be based on valid scientific evidence; • [t]he utility of the test in assessing health should be clearly stated; • [t]esting laboratories and personnel must be accredited/certified by reputable accrediting/certifying bodies for the provision of clinical genetic testing and must participate in recognized proficiency testing programs; • [g]enetic test results should be accurately labeled as medically significant or not; • [p]roviders of genetic testing must practice responsible marketing; • [o]rders for tests with medically significant implications should only be accepted from a medical professional on behalf of the individual to be tested; • [p]rofessional guidelines related to the practice of medical genetics should be adhered to, particularly with respect to genetic testing of children; • [p]rivacy and confidentiality must be addressed and maintained; and • [s]amples for tests with medically significant implications must be collected in a manner that limits the possibility of accidental or purposeful misidentification and contamination."
Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-council Policy Statement: Ethical Conduct for Research Involving Humans (2010)†	Research; Large-Scale Genetic Sequencing and Biological Specimens	"Researchers have an obligation to disclose to the participant any material incidental findings discovered in the course of research and to direct participants to a qualified professional when necessary." "[R]esearchers should develop a plan indicating how they will disclose such findings," if clinically significant incidental findings are likely. The plan should be submitted to the review board. "Researchers should be exercise caution in disclosing incidental findings that might cause needless concern;" researchers who are unsure if findings are material should consult with colleagues. "To seek consent for use of human biological materials in research," disclosure should be made about the handling of results and findings, including clinically relevant information and incidental findings. Participants should be allowed to make the choice of "whether they wish to receive information about themselves." Participants can "express whether information will be shared with biological relatives," family, community or other groups.

* Canadian College of Medical Geneticists (CCMG). (2011). CCMG Statement on Direct-to-Consumer Genetic Testing. Retrieved from http://www.ccmg-ccgm.org/documents/Policies_etc/Pos_Statements/PosStmt_EPP_DTC_FINAL_20Jan2011.pdf (formatting changed for Appendix presentation).

† Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. (2010). Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Retrieved from http://www.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf.

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
Austrian Bioethics Commission, Report of the Austrian Bioethics Commission on Internet-Based Genetic and Genome-Wide Testing (2010)*	DTC; Large-Scale Genetic Sequencing	"Tested persons must be granted access to all information pertaining to them if they so request." "Tested persons must be informed of all incidental findings that are of immediate clinical importance, or about which they have explicitly enquired. This information must be presented in a way that does not upset the tested person, especially in cases where the person has not asked for the information."
Canadian College of Medical Geneticists and Canadian Association of Genetic Counselors, Joint Statement on the Process of Informed Consent for Genetic Research (2008)†	Research; Large-Scale Genetic Sequencing	"[G]enetic counseling should be a component of the informed consent process" in all studies in which results will be disclosed. "[C]linically significant laboratory results ascertained through a research laboratory and disclosed to the research participant [should] be validated in an accredited clinical diagnostic laboratory…." "If individual results are to be disclosed, research participants should be made aware of the possibility" of incidental findings and the policy with regard to their disclosure. "Prior consent should be obtained" for disclosure.
National Council of Ethics for the Life Sciences: Portugal, Opinion on Direct Marketing of Genetic Tests to the Public (2008)‡	DTC; Large-Scale Genetic sequencing	"Genetic tests related to health should not be offered without medical indication and personalized supervision." "In case the test provides or may provide predictive health-related information, it should not be conducted unless genetic counseling is made available, before and after the results." "Health-related genetic tests for diagnostic or predictive purposes should not be made available for direct marketing to the public."
Indian Council of Medical Research, Ethical Guidelines for Biomedical Research on Human Participants (2006)§	Clinical and Research; Large-scale Genetic sequencing	"Genetic counseling should be readily available for those who are being screened." Local community representatives should be informed of the research, possible outcomes or unexpected events, and the results of the research to ensure that participants understand this information.

* Austrian Bioethics Commission. (2010). *Report of the Austrian Bioethics Commission on Internet-Based Genetic and Genome-wide Testing*. Vienna: Secretariat of the Austrian Bioethics Commission. Retrieved from http://www.bka.gv.at/DocView.axd?CobId=40383.

† Canadian College of Medical Geneticists and Canadian Association of Genetic Counselors. (2008). *Joint Statement on the Process of Informed Consent for Genetic Research*. Retrieved from http://www.ccmg-ccgm.org/documents/Policies_etc/Pos_Statements/PosStmt_EPP_CAGCInformedConsent_16Jul2008.pdf.

‡ National Council of Ethics for the Life Sciences. (2008). *Opinion on Direct Marketing of Genetic Tests to the Public*. Retrieved from http://www.cnecv.pt/admin/files/data/docs/1312230235_Portugal%20CNECV%20P056%20EN.pdf.

§ Indian Council of Medical Research. (2006). *Ethical Guidelines for Biomedical Research on Human Participants*. Retrieved from http://www.icmr.nic.in/ethical_guidelines.pdf. [Emphasis added].

AUTHOR/ ORGANIZATION, REPORT TITLE (YEAR)	CONTEXT; MODALITY	KEY POINTS
The Bioethics Advisory Committee: Singapore, Genetic Testing and Genetic Research (2005)*	Clinical and Research; Large-scale Genetic Sequencing	Pre-test counseling should include the: • "[n]ature of the condition to be tested; • [p]otential consequence of not being tested; • [f]oreseeable consequences as a result of testing…; • [t]est reliability and clinical validity…; • [t]he nature and efficacy of any interventions that might follow after genetic testing…; • [t]ype of sample required, test procedure and possible risks; • [t]urnaround time and how the results will be conveyed to the patient; • [t]reatment or management options; and • [a]lternatives to [g]enetic [t]esting and their pros and cons."
German National Ethics Council, Biobanks for Research (2004)†	Research; Large-scale Genetic Sequencing	Consent should include "the possibility or otherwise of communication of research results to the donor" and "information about the possible consequences of the communication of results of genetic analyses for the donor and his relatives." Communication of "findings must be imparted by a person with the appropriate counseling skills." Donors should be "informed in advance of the possible results, so that they could exercise their right not to know."
World Health Organization, Genetic Databases: Assessing the Benefits and the Impact on Human & Patient Rights (2003)‡	Research; Large-scale Genetic Sequencing	Disclosure of research data to participants is permissible when: • The finding has "clear clinical benefit to identifiable individual;" • "disclosure will avert or minimise significant harm to those individuals;" and • "there is no indication that the individuals in question would prefer not to know."
United Nations Educational, Social and Cultural Organization, International Declaration on Human Genetic Data (2003)§	Clinical and Research; Large-scale Genetic Sequencing	Research participants have the right to decide at the time of informed consent whether to be informed of the results of the research pertaining to their individual data. "[W]hen genetic testing that may have significant implications for a person's health is being considered, genetic counseling should be made available…."
Japanese Ministry of Health, Labour and Welfare, Ethics Guidelines for Human Genome/Gene Analysis Research (2001)¶	Research; Large-scale Genetic Sequencing	Participants must be informed of potential disease discovery. Principal investigators "must provide an opportunity for genetic counseling." If participants do not want their genetic information to be disclosed, the researcher should not disclose the information.

* The Bioethics Advisory Committee: Singapore. (2005). *Genetic Testing and Genetic Research*. Helios, Singapore: The Bioethics Advisory Committee.

† German National Ethics Council. (2004). *Biobanks for Research*. Berlin: German National Ethics Council. Retrieved from http://www.ethikrat.org/files/ner_opinion_biobanks.pdf.

‡ World Health Organization: European Partnership on Patients' Rights and Citizens' Empowerment. (2003). *Genetic Databases: Assessing the Benefits and the Impact on Human & Patient Rights*. Geneva: World Health Organization. Retrieved from http://www.codex.vr.se/texts/whofinalreport.rtf.

§ United Nations Educational, Social and Cultural Organization (UNESCO). (2003). *International Declaration on Human Genetic Data*. Retrieved from http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html.

¶ Ministry of Health, Labour, and Welfare. (2001). *Ethics Guidelines for Human Genome/Gene Analysis Research*. Retrieved from http://www.lifescience.mext.go.jp/files/pdf/40_213.pdf.

Appendix III: Guest Presenters to the Bioethics Commission Regarding Incidental and Secondary Findings

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