review

The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention?

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Advances in genomics have led to mounting expectations in regard to their impact on health care and disease prevention. In light of this fact, a comprehensive research agenda is needed to move human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. We present a framework for the continuum of multidisciplinary translation research that builds on previous characterization efforts in genomics and other areas in health care and prevention. The continuum includes four phases of translation research that revolve around the development of evidence-based guidelines. Phase 1 translation (T1) research seeks to move a basic genome-based discovery into a candidate health application (e.g., genetic test/intervention). Phase 2 translation (T2) research assesses the value of a genomic application for health practice leading to the development of evidence-based guidelines. Phase 3 translation (T3) research attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research. Phase 4 translation (T4) research seeks to evaluate the "real world" health outcomes of a genomic application in practice. Because the development of evidence-based guidelines is a moving target, the types of translation research can overlap and provide feedback loops to allow integration of new knowledge. Although it is difficult to quantify how much of genomics research is T1, we estimate that no more than 3% of published research focuses on T2 and beyond. Indeed, evidence-based guidelines and T3 and T4 research currently are rare. With continued advances in genomic applications, however, the full continuum of translation research needs adequate support to realize the promise of genomics for human health. ***Genet Med* 2007:9(10):665–674.**

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"I predict that comprehensive, genomics-based health care will become the norm, with individualized preventive medicine and early detection of illnesses."[1]

"It takes an average of 17 years for only 14% of new scientific discoveries to enter day-to-day clinical practice."[2]

In the "omics" era, expectations are mounting that advances in human genomics and related fields (e.g., transcriptomics, proteomics, metabolomics) will lead to enhanced personalized health care and disease prevention.[1,3,4] Currently, hundreds of thousands of genetic variants are being evaluated for their association with common chronic diseases.[5] Research is accelerating the use of new biomarkers derived from gene expression, proteomic, and other "omic" technologies.[6] The number of genetic tests used in clinical practice and clinical research is rising steadily.[7] In addition, family medical history is receiving renewed attention as a genomic and public health tool for disease detection and prevention.[8,9] So far, however, few human genome discoveries have led to evidence-based applications for medicine and public health.[4] Moving scientific discoveries into practice and the delivery of population-level health benefit have always been slow and difficult at best. In a study of the "natural history" of promising therapeutic or prevention interventions over a 15-year period, Contopolous-Ioannidis et al. showed that only 5% of "highly promising" basic science findings were licensed for clinical use and only 1% were actually used for the licensed indication.[10] In 2003, Lenfant lamented that basic sciences and clinical research findings are usually "lost in translation."[11] He observed that 15 years after successful clinical trials on β-blockers for patients recovering

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from myocardial infarction, these medications were prescribed for only 62% of patients. Furthermore, years after aspirin was shown to be beneficial for treating unstable angina and for secondary prevention of myocardial infarction, it was prescribed for only one third of eligible patients.[11] Renewed calls for enhancing the "translation" research enterprise have recently emerged from the National Institutes of Health as part of the Roadmap initiative,[12] as well as from the clinical, academic, and public health sectors.[2,13–17] Nearly all of these proposals highlight the role of multidisciplinary research through enhanced collaboration among researchers in the basic sciences, clinical medicine, and public health.[2,13–17]

In this manuscript, we briefly review the continuum of translation research that has been proposed for other areas of medicine and public health and apply it to genomic medicine. We propose a simple framework that classifies translation research in genomics into four types or phases of multidisciplinary research, and we offer examples. We show that only a small proportion of human genomics research has progressed from gene discovery to an evidence-based health application that has been effectively integrated into practice and has demonstrated health impact, mostly in the realm of classical Mendelian disorders. Recent findings from genome-wide association studies will open the door in the near future to more genomic applications for common complex disorders. For the latter group, it remains to be seen how these discoveries will be translated to health applications in light of complex gene-gene and gene-environment interactions. Although the ideas presented here are not unique, they have not been discussed previously in relation to genomic medicine. We hope that this discussion provides a useful agenda for translating human genomics from the "bench" to improved health outcomes for individuals and populations.

THE FOUR PHASES OF TRANSLATION RESEARCH IN GENOMIC MEDICINE

Numerous terms have been used to describe parts of the translation research enterprise, including outcomes research, clinical research, and health services research[13–19]—so many, in fact, that Kerner et al. commented, "the frequent use of the terms translational research and research translation contributes to considerable confusion as to what is being done for whom."[20] Many basic scientists believe that translation research means taking new discoveries from the laboratory to develop applications (primarily drugs) for study in human clinical trials.[21–23] Conversely, public health agencies tend to view translation research as focusing on building the evidence base for integration of applications into practice and demonstrating health impact at the population level.[24] To distinguish these phases on the translation research spectrum, some investigators refer to them as "Type 1" (translation of basic research into clinical application) and "Type 2" (clinical application to evidence-based practice guidelines).[2,25] Recently, Westfall et al.[2] proposed that the evaluation of interventions in practice can be called "Type 3 translation research." To adapt this framework to research translation in genomics, we prefer the use of the term "phase," rather than "type," and we have added a phase 4 to represent the population-level evaluation of health outcomes. We have incorporated elements of previous work in human genome epidemiology (HuGE)[26] and genetic test evaluation frameworks.[27] In this manuscript, we describe the general characteristics and types of research at each phase and provide examples (Table 1, Fig. 1). We recap definitions of some translation research terms (Table 2), and in Table 3, we summarize publication trends of human genetics and genomics translation research from 2001 to 2006. We recognize that, although the four phases of translation research can be viewed in a linear fashion, the types of research that occur during each phase can be overlapping or similar to research conducted in another phase (e.g., economic analyses, clinical trials, observational studies).

T1 RESEARCH: FROM GENE DISCOVERY TO CANDIDATE HEALTH APPLICATIONS

Gene discovery is the goal of most contemporary human genomic research. Since the completion of the Human Ge-

Table 1
The continuum of translation research in human genetics: types of research and examples

Translation research phase	Notation	Types of research	Examples
T1	Discovery to candidate health application	Phases I and II clinical trials; observational studies	Is there an association between *BRCA* mutations and breast cancer?
T2	Health application to evidence-based practice guidelines	Phase III clinical trials; observational studies; evidence synthesis and guidelines development	What is the positive predictive value of *BRCA* mutations in at-risk women?
T3	Practice guidelines to health practice	Dissemination research; implementation research; diffusion research Phase IV clinical trials	What proportion of women who meet the family history criteria are tested for *BRCA* and what are the barriers to testing?
T4	Practice to population health impact	Outcomes research (includes many disciplines); population monitoring of morbidity, mortality, benefits, and risks	Does *BRCA* testing in asymptomatic women reduce breast cancer incidence or improve outcomes?

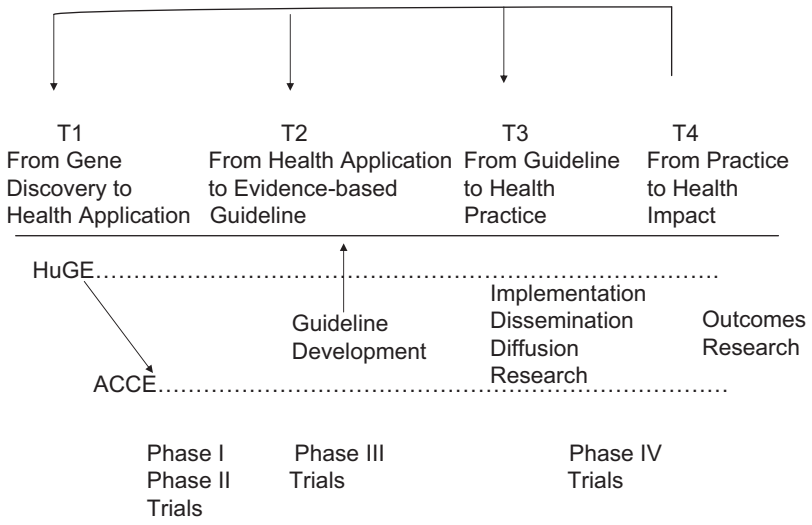

Fig. 1. The continuum of translation research in genomic medicine. HuGE, human genome epidemiology; ACCE, *a*nalytic validity, *c*linical validity, *c*linical utility, *e*thical, legal, and social issues. See text and Table 2 for definitions.

nome Project, many new methods and tools for identifying disease susceptibility genes have become available, including haplotype-tagging single nucleotide polymorphisms based on the HapMap project[28] and high-throughput technologies that allow examination of hundreds of thousands of genetic variants.[5] Collective efforts, including research networks, consortia, and biobanks[29–31] are applying these technologies in large-scale human population studies.

T1 research in genomics starts after gene discovery and has as its goal the development of a candidate application to be used in clinical and public health practice. In general, such applications are used to either support clinical evaluation (e.g., predictive testing, screening, diagnostic testing, prognostic testing) or in the selection of the most effective therapeutic options. Currently, genetic tests are used primarily for the diagnosis and management of classical genetic disorders, characterized by a clear pattern of inheritance and high penetrance.[32] Increasingly, genetic tests are being developed for predicting increased susceptibility to common diseases, modulating drug therapy (pharmacogenomics),[33] and developing prognostic indicators for treatment of cancer and other diseases.[34] Family medical history also can be considered as a predictive genomic test to identify individuals and families at risk for future disease.[9] Pharmacogenomics is an important source of new genetic applications in health practice, such as the cytochrome P450 microarray test for use in guiding selection and dosage of drugs for treating clinical depression and other disorders.[35,36] In addition, therapeutic applications include drugs that use genetic information to better target specific diseases—for example, the use of Herceptin for treatment of breast cancer.[37] The translation research pathway for therapeutics is relatively straightforward, progressing from Phase I through Phase IV clinical trials and will not be covered in depth here (Table 2). However, the pathway is less clear for genetic tests, especially because most genetic tests are still laboratory-developed (i.e., "home brew") and, therefore, not regulated by the Food and Drug Administration.[32] Even for family medical history, which is often cited as an indicator for screening or intervention in professional practice guidelines, there is no agreed-upon definition of family medical history or clear criteria that can be used as an indication for screening that might deviate from population-level recommendations.[9]

T1 research in genomics includes both observational studies and clinical trials (Table 1). We have developed two research approaches for systematically reviewing the evidence produced by such studies: (1) human genome epidemiology[26] and (2) a framework for the evaluation of genetic tests.[27] HuGE is observational, population-based research that measures the frequency distributions of alleles and genotypes in human populations, correlates genotypes with phenotypes, estimates disease risks associated with human genetic variants, and assesses gene-gene and gene-environment interactions.[26] This research is crucial for determining the clinical validity (clinical sensitivity, specificity, and predictive values) of a diagnostic or predictive genetic test. Currently, most published translation research in human genomics is in the HuGE category, which accounts for about 6% of all published articles, most of which is devoted to adult common chronic diseases (Table 3). A major challenge in this field—and a potential source of translation gridlock—is the proliferation of small studies with inconsistent results that fail to replicate initially promising findings.[38,39] In collaboration with several journals, the Human Genome Epidemiology Network[40] promotes collaborative efforts to conduct rigorous systematic reviews and meta-analyses of genetic associations; this approach can help evaluate the robustness of such associations and arrive at more precise estimates of risk (HuGE reviews).[41] More than 500 meta-analyses (including HuGE reviews) of gene-disease associations have been published within the past 6 years.[42]

An important limitation of current T1 research is that it has tended to reduce the genome to single genes/variants and has focused on a tiny portion of genomic variation, potentially

Table 2
Glossary of certain types of "translation research" involving multiple scientific disciplines

Phase 1 and 2 translation research (T1 and T2)

Many types of basic research efforts are needed to move a basic genome discovery to a potential health application. Here we highlight only those that involve observational or clinical trial studies in humans

Human genome epidemiology[26]

Research on prevalence of genetic risk factors, gene-disease associations, and gene-gene and gene-environment interactions in human populations to quantify contribution of genetic factors to human diseases and magnitude of risks

Genetic test evaluation (ACCE components)[27]

A: Analytic validity. Research to measure the ability to accurately and reliably measure the genotype of interest. The four main elements of analytic validity include analytic sensitivity (or the analytic detection rate), analytic specificity (or 1- the analytic false positive rate), laboratory quality control, and assay robustness

C: Clinical validity. Research to measure the test's ability to detect or predict the associated disorder (phenotype)

C: Clinical utility. Research to define the risks and benefits associated with a test's introduction into practice. Specifically, clinical utility focuses on the health outcomes (both positive and negative) associated with testing

E: Ethical, legal, and social issues (some view this component as part of clinical utility). Research to assess concerns specific to genetic information, such as implications for relatives of the person undergoing testing, the possibility of insurance discrimination, and stigmatization based on genotype

Clinical trials[43]

Phase I: Research on a new drug or treatment in a small group of people (20–80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects

Phase II: The study drug or treatment is given to a larger group of people (100–300) to see whether it is effective and to further evaluate its safety

Phase III: The study drug or treatment is given to large groups of people (1000–3000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely

Phase IV: The postmarketing studies delineate additional information, including the drug's risks, benefits, and optimal use

Phase 3 translation research (T3)

Dissemination research: Systematic study of how the targeted distribution of information and intervention materials to a specific health audience can be successfully executed so that increased spread of knowledge about the evidence-based interventions achieves greater use and impact of the intervention[24]

Implementation research: Systematic study of how a specific set of activities and designed strategies are used to successfully integrate an evidence-based intervention within specific settings (e.g., primary care clinic, community center, school)[24]

Diffusion research: Systematic study of the factors necessary for successful adoption by stakeholders and the targeted population of an evidence-based intervention that results in widespread use and specifically includes the uptake of new practices or the penetration of broad-scale recommendations through dissemination and implementation efforts, marketing, laws and regulations, systems-research, and policies[24]

Phase 4 translation research (T4)

Outcomes research: Research that describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions on "final" endpoints that matter to decision makers. Decision makers may include patients, families, individuals at risk, provider, private and public payers, and so forth[18]

missing the value of looking across the genome. Hence, an undue emphasis on meta-analyses of published candidate genes studies may miss the currently emerging data in high powered studies of genome-wide associations. In the long run, current approaches have to be supplemented with genome-wide approaches involving systems biology in large-scale well-conducted epidemiologic studies.

An important application of HuGE research is for the evaluation of clinical validity of complex genetic tests (T2 research discussed below). An emerging example of T1 research is the construction of "genomic profiles" (e.g., "cardiogenomic" profile, "osteogenomic" profile), testing combinations of genetic variants to predict increased risk of common diseases and potentially guide interventions.[44] Although most genomic profiles are considered far from ready for clinical use,[45] some companies have already developed and marketed them (in some cases, directly to consumers) for use in disease prevention and health promotion. Janssens et al. (personal communication) have clearly demonstrated the many knowledge gaps that exist in this area. They examined genomic profiles marketed by seven different companies, which together included at least 73 different polymorphisms in 56 genes. No meta-analyses had been published for variants in 24 of these genes (43%), and meta-analysis results were statistically significant for only one third of the remainder, most finding relatively modest associations (odds ratios between 1 and 2) (Janssens et al., personal communication). A further limitation to the use of genomic profiling is that meta-analysis of data on individual genetic variants in a profile can only provide a partial picture of the complex interaction between genetic variants and gene-environment interactions. Paradigms for how to synthesize this more complex information for health practice are only beginning to be discussed and have no current standard methodologic guidance.

Finally, it is important to distinguish methods for evaluating random genetic markers from those used to establish functional effects of individual identified variants. Of course, the latter currently numbers no more than 50–100 variants. The idea of testing (combinations or large panels of) markers is inherently different (discovery tools) than testing functional variants.

T2 RESEARCH: FROM HEALTH APPLICATION TO EVIDENCE-BASED GUIDELINES

The development and evaluation of genomic applications for use in practice is a challenging and mostly unregulated process. Government advisory groups have spelled out the need for thorough evaluation of tests and development of evidence-based guidelines for their use.[32,46] In 1997, the Task Force on Genetic Testing first outlined a three-step process for evaluation of genetic tests based on the assessment of analytic and clinical validity and clinical utility.[46] The 2000 report of the Secretary's Advisory Committee on Genetic Testing added an emphasis on social issues, leading to a four-step process repre-

Table 3
Numbers of publications related to human genetics and genomics, observational studies, clinical trials, practice guidelines, and research on genetic tests, 2001–2006

Year	Total[a]	Human genome[b] epidemiology	Clinical[a] trials	Practice[a] guidelines	Genetic test[b] evaluations
2001	54,521	2,398	942	25	119
2002	55,452	3,147	927	21	213
2003	58,813	3,460	1,242	23	311
2004	63,251	4,330	1,341	34	379
2005	66,945	5,243	1,586	26	491
2006	64,187	5,497	1,578	34	462
Total	363,169	24,075	7,616	163	1,975
Percentage	100	6.6	2.1	0.04	0.5

[a]Query conducted on PubMed April 16, 2007,[47] on genetics and genomics (limited to humans). Special online checkboxes were used to identify clinical trials and practice guidelines using National Library of Medicine criteria without further review by the authors.
[b]Query conducted on April 16, 2007, on the Centers for Disease Control and Prevention's GDPinfo database, an extensively curated database.[48] Publications chosen were on human genome epidemiology and various aspects of genetic tests evaluation, newborn screening, health services research, laboratory practice, and economic evaluation.

sented by the acronym ACCE (for *a*nalytic validity; *c*linical validity; *c*linical utility; and *e*thical, legal, and social implications).[32] This type of evaluation depends on research in multiple disciplines, including clinical medicine, laboratory sciences, economics, public health, ethics, and behavioral and social sciences. The ACCE model project, sponsored by the Centers for Disease Control and Prevention (CDC), developed a framework for evaluation that incorporates the four proposed components of evaluation to address T2 research. The ACCE project has been discussed extensively elsewhere[27,49] (Appendix); here, we summarize it only briefly.

The translation of a genetic test from research into practice starts with identification of the disorder (or pharmacogenetic effect) tested for, the specific test to be used, and the clinical scenario in which the test will be used (e.g., diagnosis versus predictive, population to be tested). A test must be evaluated for each clinical application or intended use. Evaluation often begins with establishment of analytic performance characteristics (analytic sensitivity, analytic specificity, and assay robustness).[50] Analytic validity is often difficult to assess, because the relevant data are rarely published. Once a test is in use, additional data can sometimes be collected through proficiency-testing programs, such as that conducted jointly by the College of American Pathologists and the American College of Medical Genetics.[50] Clinical validity is usually established in observational studies of genotype-phenotype association (which we describe as T1 research); when correctly designed and conducted, such studies can be used to estimate the clinical sensitivity and specificity of a genetic test and—if the study is population-based—its positive and negative predictive value. Genetic tests used to guide therapy (i.e., pharmacogenetic tests) also may be evaluated in clinical trials (Table 2). In general, T2 research on genetic tests begins once analytic validity has been established and the early results of clinical validity look promising to test developers.

T2 research—which for now is largely focused on the translation of new genetic tests, but may include family health history tools (see below)—also includes the evaluation of benefits and risks on a larger scale, which is necessary for evaluating the clinical utility of testing in the context of a wide range of ethical, legal, and social issues. The end result of such research is systematic review and synthesis that will support the development of evidence-based practice guidelines. This research phase can take a long time, especially for rare genetic diseases, for which it is difficult to accumulate and synthesize the evidence. Currently, most T2 research in human genomics is inconsistent and nonsystematic. As shown in Table 3, only 2% of research publications in this field have been classified by the National Library of Medicine (in PubMed) as reports of clinical trials, most of which are not randomized trials. During the same time period, only 0.5% of human genetic studies were classified by the CDC database as genetic test-related. National Library of Medicine listed 163 "guidelines" in human genetics published during the past 6 years (see query details in Table 3). Guidelines on several genetic tests have been issued by diverse groups, including professional societies, ad hoc consensus groups, government agencies, and advocacy organizations. Of course, the process of guideline development is not standardized, and many guidelines are developed on the basis of expert opinion, often in the absence of complete information. One rigorous approach to guideline development based on systematic evidence review is conducted by the US Preventive Services Task Force (USPSTF) hosted by the Agency for Health Care Research and Quality.[51,52] From 2001 to 2006, the USPSTF database added only two evidence-based guidelines in genetics: one on population- and risk-based testing for hereditary hemochromatosis (HHC)[53] and one on *BRCA1/2* testing for hereditary breast and ovarian cancers.[54] To respond to the need for evidence-based guideline development in genomics, CDC launched in 2004 the Evaluation of Genomic Applica-

tions in Practice and Prevention initiative, which is currently supporting evidence reviews and the development of evidence-based recommendations on seven genomic applications for health practice.[55]

HHC, which is a useful example for illustrating the continuum of T1 and T2 research, is the most common form of hereditary iron overload disease in the United States.[56] The *HFE* gene and two common point mutations associated with HHC (*C282Y* and *H63D*) were discovered in 1996, initiating a debate on the value of population genetic screening for this disease, because a simple intervention (regular phlebotomy) is effective in reducing the risk of adverse health outcomes.[57] Soon after these discoveries, a genetic test identifying them was developed and promoted for use. During 1997, CDC and the National Human Genome Research Institute jointly sponsored an expert panel workshop to consider the use of *HFE* genetic testing for early detection of HHC. The panel concluded that population screening for mutations in *HFE* could not be recommended because of uncertainty about the natural history of the disease (especially age-related penetrance), optimal care for asymptomatic persons who are found to carry mutations, and the psychosocial and societal impact of genetic testing.[58]

Publication of the workshop report was followed by several years of extensive T1 and T2 research. For example, a population-based, nationwide survey established that almost 5% of the United States' non-Hispanic, white population was homozygous or compound heterozygous for the *C282Y* and *H63D* mutations.[59] However, epidemiologic analysis of the burden of disease using hospital records[60] and death certificates[61] found that the prevalence of diagnosed disease is much lower, suggesting that penetrance is low. A meta-analysis of the association of *HFE* mutations with the risk of clinical disease showed that homozygosity for the *C282Y* mutation was associated with the highest risk of HHC, whereas risks associated with other genotypes, including *C282Y/H63D* and *H63D/H63D*, were much lower.[62] A large National Institutes of Health-funded cohort study in the Kaiser Permanente Southern California health care network suggested that disease penetrance for *HFE* mutations may be quite low[63]: only 1 of the 152 subjects who were homozygous for *C282Y* had HHC symptoms. This finding, along with other data, led the USPSTF in 2006 to recommend against routine population genetic screening for hemochromatosis.[53] Thus, 10 years after the discovery of the *HFE* gene and its mutations, intensive T1 and T2 research studies led to an evidence-based recommendation against population genetic screening for HHC.

Lastly, family medical history tools have been evaluated as a type of predictive test using the ACCE framework.[9] Family history criteria (e.g., number of affected relatives, age at disease onset) are being examined for their association with common diseases and their ability to predict future disease.[64,65] These criteria are then included in risk assessment schemes or family history tools developed to identify people at increased risk for common diseases such as heart disease, diabetes, and cancer.[9,66]

T3 RESEARCH: FROM EVIDENCE-BASED GUIDELINES TO HEALTH PRACTICE

The translation of evidence-based guidelines into practice is one of the most challenging problems in health care and disease prevention. The Institute of Medicine focused on this problem in its report "Crossing the Chasm: A New Health System for the 21st Century," which summarized the difficulty of effective implementation and diffusion of proven health care interventions.[67] This gap is especially problematic in preventive medicine, which is a growing focus of genomic research.[68] Despite extensive public health research on the efficacy and effectiveness of health promotion and disease prevention strategies, methods for disseminating these interventions and encouraging their implementation and widespread adoption are not well developed or evaluated.[69] T3 research addresses such issues as increasing the spread of knowledge about evidence-based interventions (dissemination research), integrating these interventions into existing programs and structures (implementation research), and widespread adoption of these interventions by stakeholders (diffusion research)[24] (Table 2).

The "lost in translation" problem is complicated by the increasing cost of health care and the persistent inequities in access. At a 2004 Institute of Medicine meeting on the implications of genomics for public health, William Foege, a prominent public health leader, expressed concern that genetics could exacerbate health disparities: "The challenge to genomics is to overcome inequitable allocation of benefits, the tragedy that would befall us if we made the promise of genetics available only for those who could afford it and not for all society."[70] Policymakers, funding agencies, and researchers are beginning to recognize the need for a translation research agenda that extends beyond the "bench-to-bedside" paradigm.[2,22,24] Some people have called for public-private collaborations to support this T3 research agenda, which has until now received little public investment.[2,14] Additional challenges include workforce training, public health literacy, information systems, and public participation.[14,15] These problems, which are pervasive throughout our health care system, are likely to worsen as new genome-based technologies enter clinical practice.

Currently, few genetic and genomic applications are ready for implementation in routine clinical practice. A notable exception is breast cancer susceptibility gene (*BRCA*) mutation testing for predicting breast and ovarian cancers, for which the USPSTF issued two evidence-based recommendations during 2005.[54] First, the Task Force recommended "against routine referral for genetic counseling or routine breast cancer susceptibility gene (*BRCA*) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*)." However, the USPSTF also recommended that "women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for *BRCA* testing."[54] It is noteworthy that in this particular guideline, the USPSTF spelled

out clearly what family history criteria warranted the referral for counseling and possible testing.

The story of *BRCA1* illustrates the complex character of translation research. Discovered in 1994, *BRCA1* was the first major susceptibility gene to be linked to a common disease. A gene patent application was filed the same year, and a genetic test became commercially available in 1996. T1 research was conducted largely by the corporate laboratory holding the patent, and the data are proprietary.[71] T2 research is unfinished; authors of the systematic evidence review conducted for the USPSTF observed that "no data describe the range of risk associated with *BRCA* [*BRCA1* and *BRCA2*] mutations, genetic heterogeneity, and moderating factors; studies conducted in highly selected populations contain biases; and information on adverse effects is incomplete."[72] T3 research studies have been published in relation to various recommendations for screening, counseling, and treatment for women with these mutations.[73] During 2003, a pilot direct-to-consumer marketing campaign for *BRCA1* and *BRCA2* testing provided an opportunity to study diffusion of knowledge (although not evidence-based guidelines).[74] A survey of approximately 1000 randomly selected family physicians, internists, obstetrician-gynecologists, and oncologists found that their knowledge of genetic testing for susceptibility to breast and ovarian cancers was similar, whether or not they practiced in a city that received the pilot marketing campaign; however, those of them who were aware of relevant professional practice guidelines were significantly more knowledgeable than the other health professionals in the survey.[75] Other controlled clinical trials have reported on enhancing patient education and information about options for genetic testing for breast and ovarian cancers using various forms of decision aids.[76–79]

Kerner et al. points out that most dissemination research is "conducted in the relatively resource-rich infrastructures of either academic medical centers or the biomedical industry."[20] How findings of such studies might apply to other populations—especially underserved populations—is largely unknown. Westfall et al. identified several major challenges to research in this area, including the heterogeneous character of primary care; the lack of successful models for collaboration among academic researchers, community physicians, and patients; and "the failure of the academic research enterprise to address needs identified by the community."[2] Furthermore, T3 research has focused largely on individual behavior change by health care providers and patients, although, as McBride has observed, "three decades of research in developing and testing behavior-change interventions for risk reduction tell us it is unlikely that a genetic test result alone will prompt behavior change."[80] Translation research also must address the integration of genetic testing with existing, evidence-based interventions in specific settings (implementation research). Perhaps even more important is research at the level of health and social systems (diffusion research), addressing such factors as the influence of marketing, laws and regulations, and policymaking by professional organizations, insurers, and other stakeholder groups. T3 research is inherently nonlinear, requiring wide-ranging excursions down the collateral networks of the "blue highways" described by Westfall et al. to understand the transfer of genetic knowledge among individuals, providers, health care systems, and the public health community.[2] T3 research points to the complexities of compliance and education that can ultimately affect the clinical utility of a genetic test in the "real" world as opposed to the inherent clinical utility of the test done under ideal scenarios of controlled clinical trials.

T4 RESEARCH: FROM PRACTICE TO POPULATION HEALTH IMPACT

The last phase of translation research assesses how the adoption of evidence-based recommendations and guidelines can make an impact on real-world health outcomes. A workshop sponsored by the National Cancer Institute suggested a broad definition of "outcomes research" as that which "describes, interprets and predicts the impact of various influences, especially (but not exclusively) interventions of 'final' endpoints that matter to decision makers. The decision makers may include patients, families, individuals at risk, providers, private and public payers and purchasers, regulatory agencies, health care accrediting organizations, and society at large."[18] In this manuscript, we refer to research focused on clinical and public health outcomes as T4 research to distinguish it from research focused on implementation processes (T3), although the two are intertwined. Lipscomb et al. describe several approaches to studying outcomes related to cancer control at different levels, which they label "macro," "meso," and "micro."[18] For example, macro-level outcomes research includes public health surveillance of disease incidence, morbidity and mortality, and health-related quality-of-life indicators in populations defined by geographic and demographic categories. Meso-level outcomes research includes clinical decision modeling and cost-effectiveness analysis as well as studies monitoring quality of care. Micro-level outcomes research examines individual interactions between providers and patients to describe risks and benefits outside the context of randomized clinical trials.[18]

We use newborn screening as an example to illustrate T4 research. In the United States, state-mandated programs have tested all newborns for genetic conditions for several decades.[81] This system has been increasingly under pressure as states consider the addition of dozens of new "conditions" to the newborn screening panel, because new laboratory methods (tandem mass spectrometry [MS/MS]), make it technically straightforward to do so.[82] A case in point is newborn screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD), a disorder of fatty acid metabolism, for which the impact of early detection has been debated.[83] A systematic review and decision analysis that compared newborn screening with clinical diagnosis in the Canadian context concluded that "screening consumes more resources than no screening but attains better health outcomes."[84] Wilcken et al.[85] recently provided new evidence for the effectiveness of MCADD screening. They studied almost 2.5 million children born in Australia between 1994 and 2004; approximately one third of these chil-

dren were screened for MCADD at 2–3 days of age. The study found a clear reduction in mortality among children in the screened group (4%) compared with children who were diagnosed through clinical presentation or after diagnosis of a sibling (17%). Ideally, studies establishing the utility of an intervention should be conducted and evidence-based guidelines developed before a program is implemented; however, this example demonstrates that even when this does not occur, ongoing data collection and analysis can be valuable for filling in information gaps.[86]

CONCLUDING REMARKS

We have presented an overarching framework for translation research for moving promising genomic applications to clinical and public health practice for population health benefit. We have discussed some types of research needed during each phase, and we have stressed the importance of developing evidence-based guidelines. Although it is difficult to estimate how many genetic studies examined in T1 research will be sufficiently promising to be considered for further development, we estimate that no more than 3% of research published in this field so far focuses on T2 research and beyond. Indeed, evidence-based guidelines and T3 and T4 research are very rare. We urge government, academia, industry, public health, and community groups to join forces in guiding the genomics research translation enterprise, making optimum use of blue highways (not just the fast lane) and avoiding the "myriad detours, speed traps, roadblocks and potholes" that Westfall et al. cautioned against.[2]

Appendix

Translation research questions related to the evaluation of genetic tests under the ACCE framework[27]

Element	Component	Specific question
Disorder/Setting		1. What is the specific clinical disorder to be studied?
		2. What are the clinical findings defining this disorder?
		3. What is the clinical setting in which the test is to be performed?
		4. What DNA test(s) are associated with this disorder?
		5. Are preliminary screening questions employed?
		6. Is it a stand-alone test or is it one of a series of tests?
		7. If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results (series)?
Analytic validity	Sensitivity	8. Is the test qualitative or quantitative?
		9. How often is the test positive when a mutation is present?
	Specificity	10. How often is the test negative when a mutation is not present?
		11. Is an internal quality control program defined and externally monitored?
		12. Have repeated measurements been made on specimens?
		13. What is the within- and between-laboratory precision?
		14. If appropriate, how is confirmatory testing performed to resolve false-positive results in a timely manner?
		15. What range of patient specimens has been tested?
		16. How often does the test fail to give a useable result?
		17. How similar are results obtained in multiple laboratories using the same, or different technology?
Clinical validity	Sensitivity	18. How often is the test positive when the disorder is present?
	Specificity	19. How often is the test negative when a disorder is not present?
		20. Are there methods to resolve clinical false-positive results in a timely manner?
	Prevalence	21. What is the prevalence of the disorder in this setting?
		22. Has the test been adequately validated on all populations to which it may be offered?
		23. What are the positive and negative predictive values?
		24. What are the genotype/phenotype relationships?
		25. What are the genetic, environmental, or other modifiers?
Clinical utility	Intervention	26. What is the natural history of the disorder?
	Intervention	27. What is the impact of a positive (or negative) test on patient care?
	Intervention	28. If applicable, are diagnostic tests available?
	Intervention	29. Is there an effective remedy, acceptable action, or other measurable benefit?

(*Continued*)

Appendix
Continued

Element	Component	Specific question
	Intervention	30. Is there general access to that remedy or action?
		31. Is the test being offered to a socially vulnerable population?
	Quality assurance	32. What quality assurance measures are in place?
	Pilot trials	33. What are the results of pilot trials?
	Health risks	34. What health risks can be identified for follow-up testing and/or intervention?
		35. What are the financial costs associated with testing?
	Economic	36. What are the economic benefits associated with actions resulting from testing?
	Facilities	37. What facilities/personnel are available or easily put in place?
	Education	38. What educational materials have been developed and validated and which of these are available?
		39. Are there informed consent requirements?
	Monitoring	40. What methods exist for long-term monitoring?
		41. What guidelines have been developed for evaluating program performance?
ELSI	Impediments	42. What is known about stigmatization, discrimination, privacy/confidentiality, and personal/family social issues?
		43. Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?
	Safeguards	44. What safeguards have been described and are these safeguards in place and effective?

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