# Ethical Issues in Genetics Research

Benjamin S. Wilfond MD

Director, Treuman Katz Center for Pediatric Bioethics
Seattle Children's Hospital

Professor and Head, Division of Bioethics
Department of Pediatrics, University of Washington School of Medicine

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# Genetics Research Objectives

- Natural history studies
  - Description of phenotype
  - Genotype/phenotype correlation
- Environmental studies
  - Physical environment
  - Social environment
- Social science studies
  - Assessments of knowledge, attitudes, and behavior
- Intervention studies
  - Behavioral interventions
  - Pharmocogenomics
  - Gene transfer

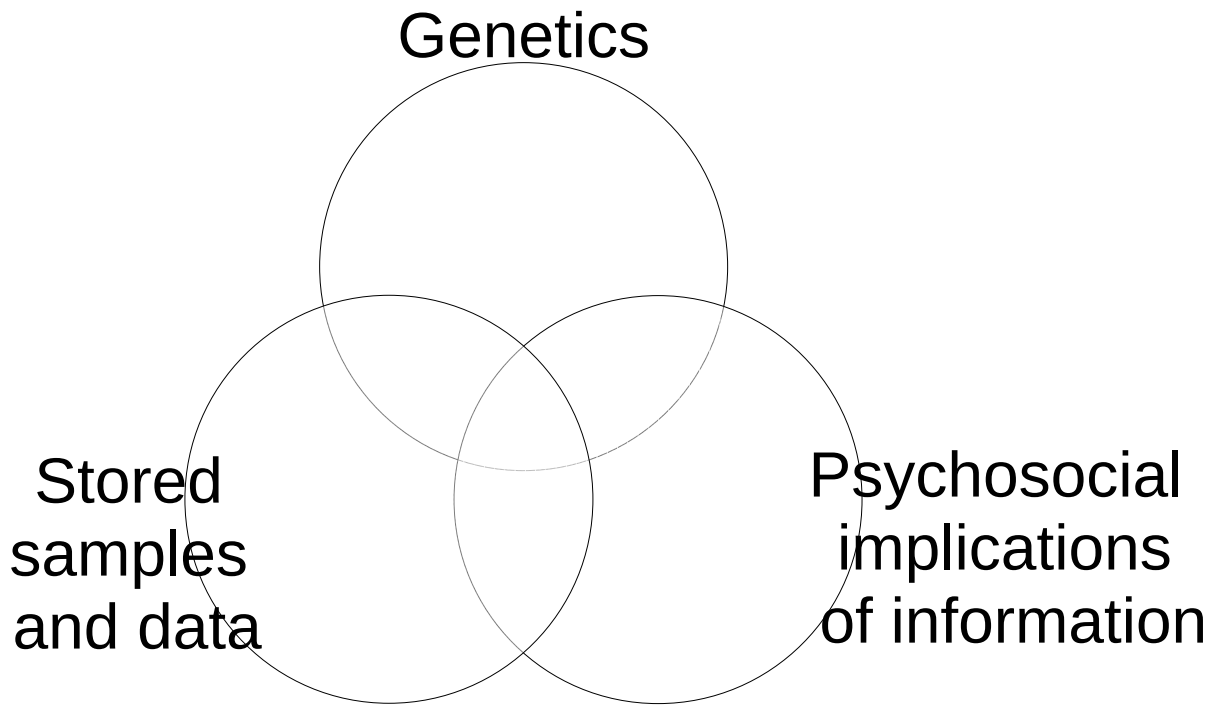
# Genetics Research Approaches

- Recruitment approach
  - Family based studies
  - Population based studies

- Sample approach
  - Prospective collection
  - Archived biological specimens/medical information

- Laboratory approach
  - Genome (Genome Wide Associations)
  - Genotype (DNA)
  - Gene expression (RNA)
  - Gene products (proteins, etc)

# Is genetics research special?



# Important (but not unique) characteristics of genetic information

- Complex and uncertain information
- Special cultural meaning
- Familial implications
- Reproductive decision-making impact
- Primarily psychosocial risks

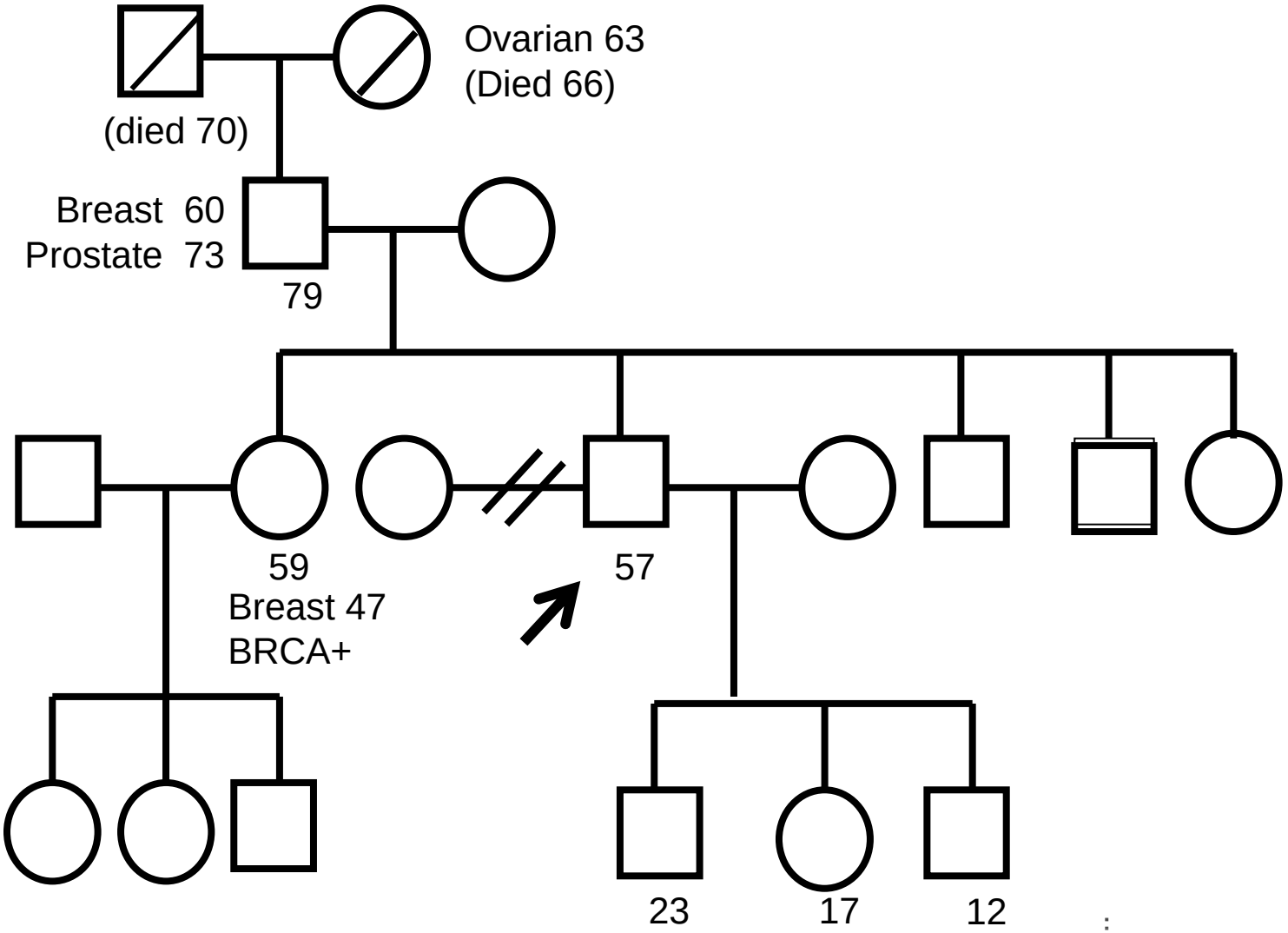
# Sharing information in the family

- Several generations of a family are enrolled in a study that will provide them with BRCA results
- The researchers promise that each person's test results will be confidential

# Sharing information in the family

- BRCA
  - Autosomal dominant gene
  - 5% of all breast cancer
- People with BRCA mutations
  - 50-85% chance of developing breast cancer
  - Increased risk of ovarian and male breast cancer
- Reducing risk of breast cancer
  - Surveillance
  - Surgical and chemopreventive interventions

# Sharing information in the family

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# Sharing information in the family

- Prior to testing, he states that
  - He wants to protect his father from feelings of "transmission guilt"
- He IS a BRCAcarrier
  - He tells the researchers that he will let his daughter know he is a carrier "when the time is right"
  - We hear from his niece that he has told the father he tested negative
- The research team is worried that he will not disclose that his daughter is at risk and should consider BRCA testing
  - She will assume that she is negative and forgo testing and surveillance

# Ethical dilemma

- How do the researchers balance their obligation to protect the confidentiality of the father with a duty to inform the daughter to avoid harm?
  - Not clear whether or not there has been a disclosure
  - There is time to have further discussions with father

- Is there a obligation to disclose the father's results to the daughter?
  - How should the fact that the father misled the daughter rather than merely not disclose his status influence the obligation?

# Duty to disclose

- Serious harm
- Likely harm
- Avoidable harm
- No reasonable alternatives

President’s Commission 1983

# The potential harms in genetic research are primarily related to *sharing genetic information*

- Intended sharing of information
- Unintended sharing of information
- No sharing of information

# Disclosure of information

- Intended Disclosure
  - Complex and uncertain information
  - Confusion
  - Anxiety
  - Familial implications
  - Stigmatization
  - Discrimination
- Unintended Disclosure
  - Above concerns
  - Privacy
- No Disclosure
  - Community harms
  - “Harmless wrongdoing”

# Familial implications

- Unknown family relationships (adoption, paternity)
- Adult children
- Twins
- Willingness to contact relatives
  - Proband vs investigator

# Community Harms

- Adverse effects of genetic information on communities
  - Reinforces cultural stereotypes
  - Feelings of exploitation
- What counts as a community?
- Who speaks for a community?
- What role should communities have?

# Harmless Wrongdoing

- No attributable adverse consequence (unlinked samples) but still may be concerns about participation without consent
  - Curiosity
  - Privacy
  - Object to research objectives
  - Object to contributing to potential profit

- Reasons for not obtaining consent:
  - Impractical (people have moved)
  - May be upsetting to contact subject
  - Too much effort
  - Might not give consent

- Challenge
  - Balancing these concerns with value of research

J Feinberg, 1990

# Balancing Genetic Research

Benefits to Society and Subjects

Risks of Harms to Subjects and Society

Protections

Study Design

Oversight and Consultation

Informed Consent

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# Protections in Genetics Research

- Design study to minimize risks
  - Reduce psychosocial impact related to disclosure of information
    - Nondisclosure of some data
    - Genetic counseling/education when disclosing data
  - Confidentiality of information
    - Non-linkage of samples/data with identifiers
    - Database encryption for linked samples/data
- Oversight
  - Community engagement in protocolv development
  - IRB review
- Informed consent


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# How should we decide about which individual results to disclose to participants?

- Cytochrome P450 in an asthma treatment clinical trial?
- Apo E4 in an Alzheimer's disease prevention clinical trial?
- BRCA in a population-based cross-sectional epidemiological study?
- Results of completely undetermined significance(i.e. first study using a particular marker) in a longitudinal epidemiological study?

# Three approaches to data disclosure

- Research - focused
- Autonomy - focused
- Result - focused

Ravitsky and Wilfond, AJOB 2006

# Research - focused approach

- Rationale
  - Goal of research is to provide generalizable knowledge to benefit society
- Approach
  - Results should generally not be offered
    - Exceptions based on extraordinary clinical value
- Objections
  - There are other responsibilities to participants

# Autonomy - focused approach

- Rationale
  - Individuals should have access and control of information about them
- Approach
  - Results should generally be offered
    - Unless clearly harmful to participants
- Objections
  - Conflates research with clinical care
  - Not clear what “data” count as information

# Result - focused approach

- Approach depends on
  - Informational considerations
  - Relational considerations

- Rationale
  - Takes a range of values into account

# Underlying values must be balanced

- Beneficence
  - Obligation to offer results when likely to be helpful
  - Obligation to not offer when likely to be harmful

- Respect
  - Obligation to respect preferences both to receive and not receive results (i.e. offer rather than disclose)

- Reciprocity
  - Obligation to respect preferences for results based on the contribution to research

- Justice
  - Obligation to prioritize resource utilization associated with disclosure with obligations to society to conduct further research

# Results focused approach

- Objectives
  - To help investigators determine approach for study design
  - To help IRBs evaluate study design

- Outcomes
  - Offer results
    - Allows for persons to decline results
    - Include appropriate laboratory quality and counseling
  - Refer for commercially/clinically available results
  - Do not offer results
    - Inform about aggregate results

- Discretion
  - In some cases, there is no single correct approach (or overiding value) and IRBs and investigators have discretion
  - Important for IRBs to exercise flexibility for discretionary circumstances

# nformational considerations

- Analytic Validity
- Clinical Utility
- Personal Meaning
- Clinical Validity

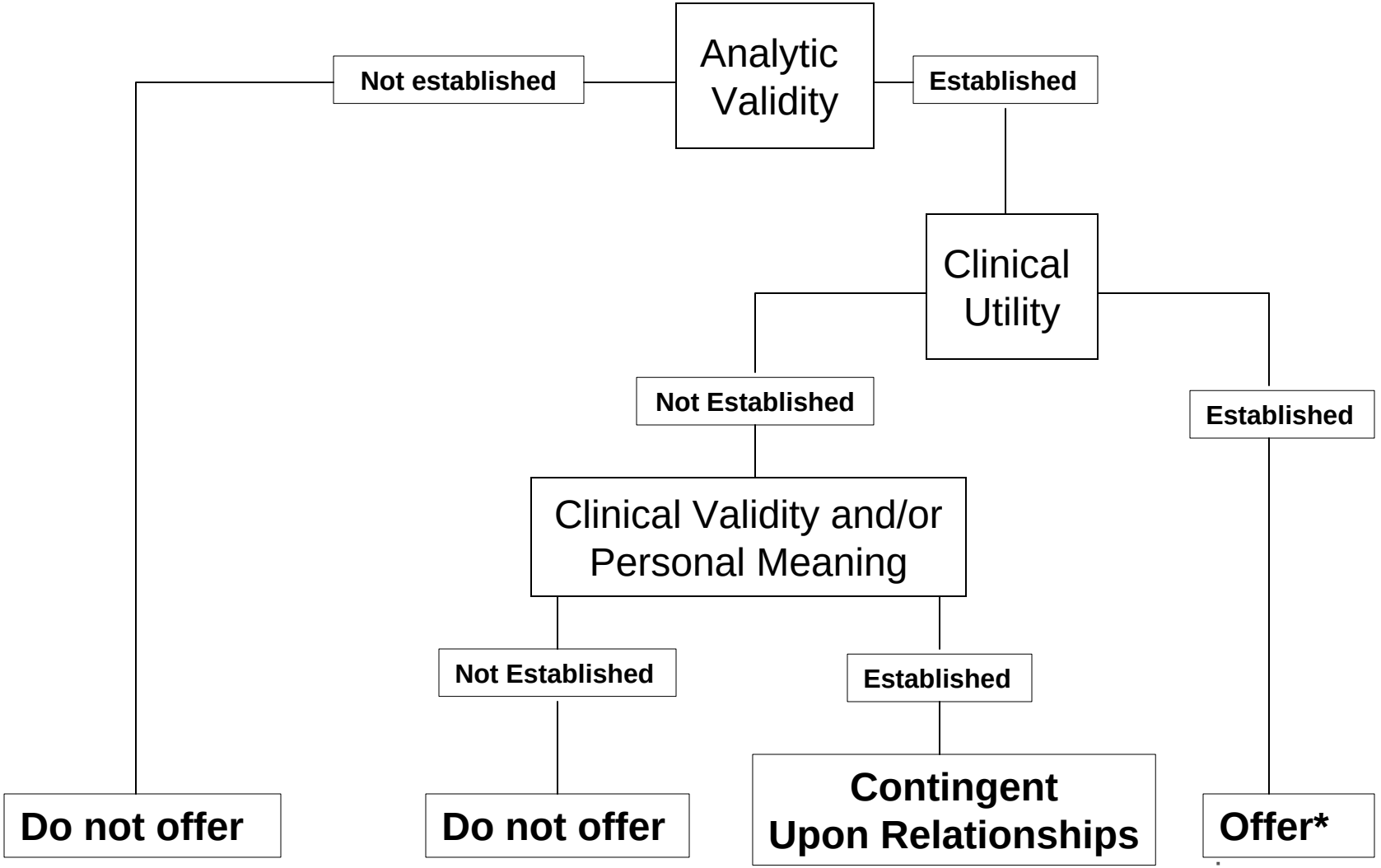
# Relational considerations

- Nature of the relationship between investigators and participants
- Investigators' capacities to offer results safely and effectively
- Alternative access for participants

# The Result – Focused Approach and relationships

- When clinical utility is established
  - Relationships can guide the specific approach to offering results
- When clinical utility is not established, and depending on personal meaning and clinical validity
  - Relationships can guide whether to offer results
- A flexible approach
  - Approach for particular result will vary with the relationships
  - With the same relationships, different results (based on informational considerations) will be approached differently
  - Not all relational considerations are relevant in all cases

# Informational Considerations

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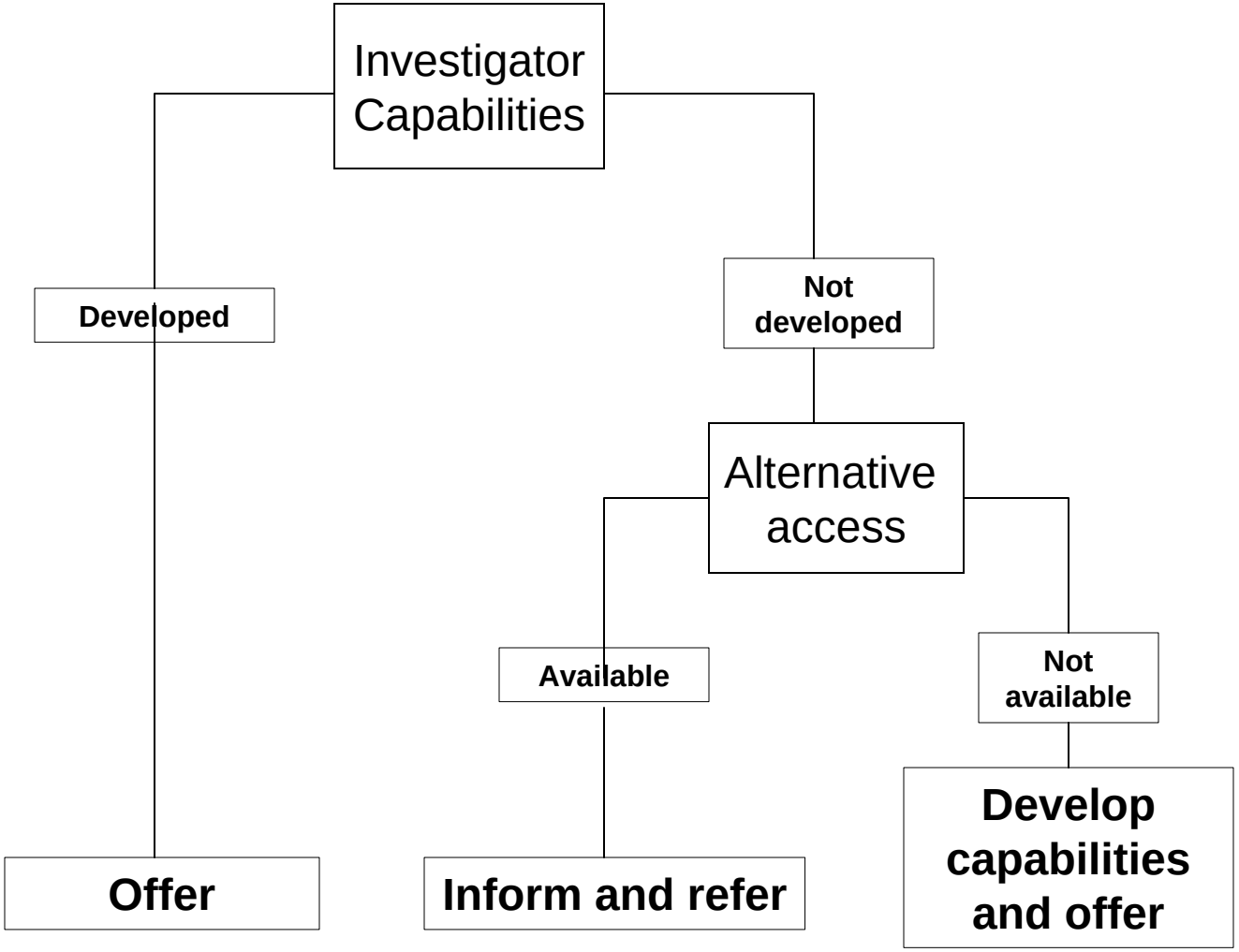
# Relational considerations when analytic validity and clinical utility are established

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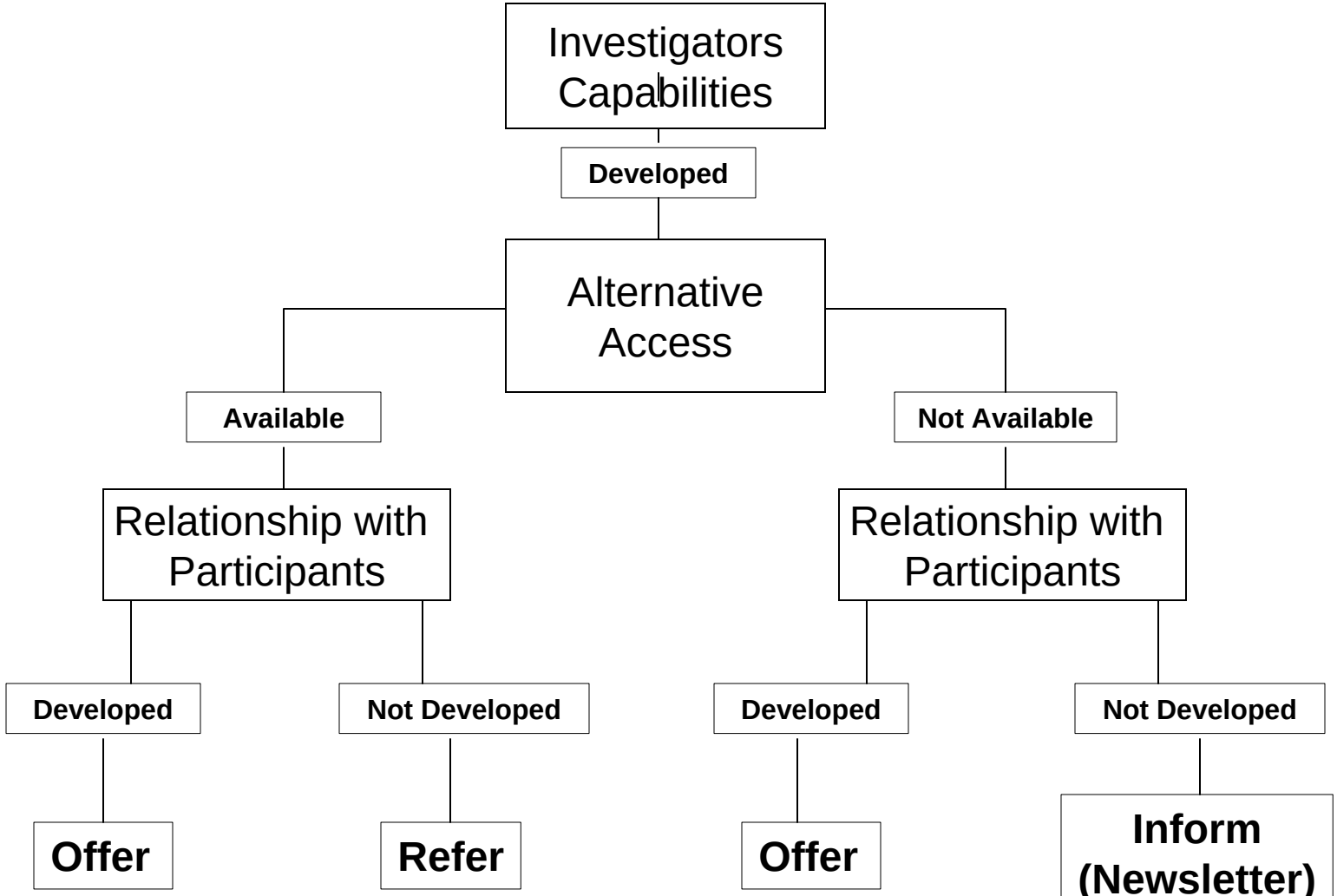
# Relational considerations for results with personal meaning, but clinical utility is not established

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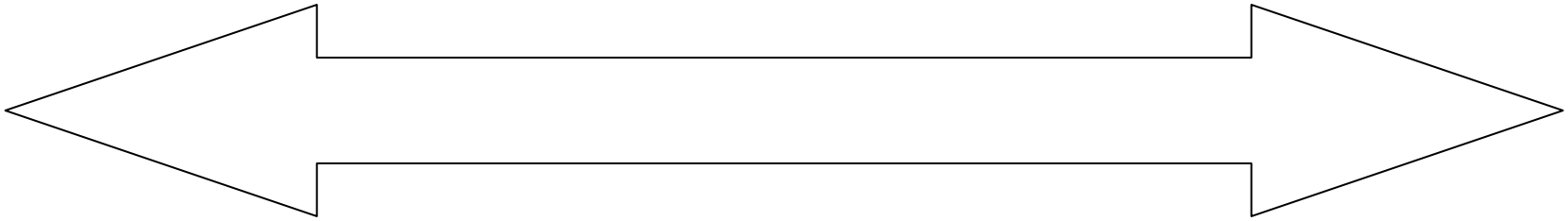
# Informed consent

- What information is necessary to disclose for informed consent to be “valid”?



Any genetic research

Specific disease

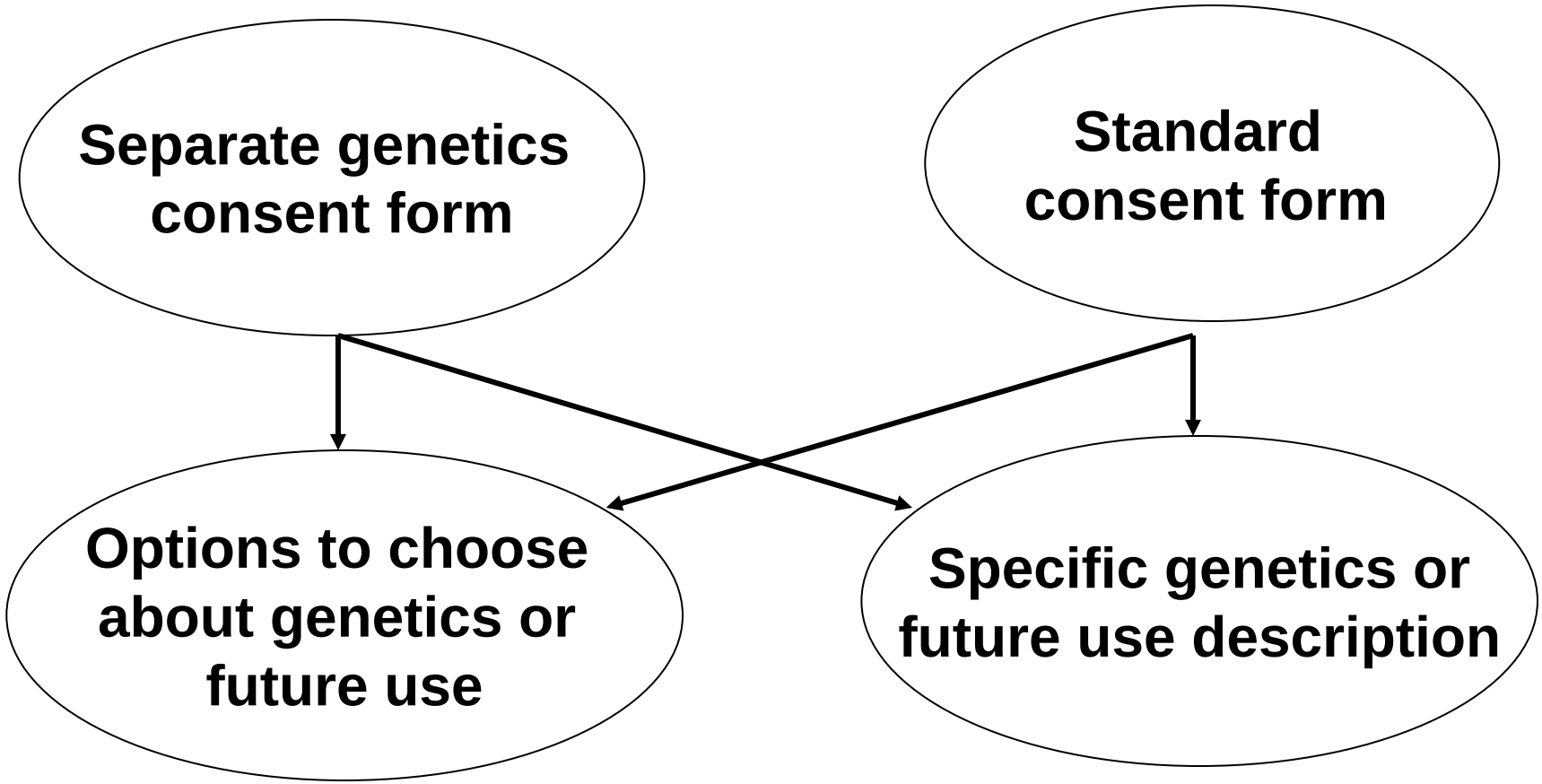
Particular gene

Explicit methodology

Individual investigator

Distinct time frame

# The genetics consent menu: à la carte or prix fixe



# Reasons for à la carte consent (specific consent)

- Respects people's preferences
- Facilitates understanding
- Increases enrollment
- Clarifies study design

# Reasons for prix fixe consent (blanket consent)

- Most people don't have strong preferences
- Genetics research *is* a specific research scope
- Options may be confusing to understand
- Need to prioritize this information with other information about the study to facilitate understanding
- People may change mind or not fully appreciate the significance when they make decision

# Improving consent forms to enhance decision-making

- Clarify the purpose of the consent form
  - Decision making tool
- Tailor information to particulars of study
- Prioritizing information to improve decision-making
  - Consider what information to provide in supplemental materials
  - Consider what information should be discussed in the protocol but not in the consent form

# Study protocol or consent form?

- Determine the ethical design and describe this in the study protocol
- Use the consent form to communicate relevant aspects of the design
  - Newsletters and websites can also be useful
- Avoid using the consent form to specify or clarify the design

# What is the scope of parental permission?

1. Is it acceptable to begin research with children's data/samples without *their* consent and just parental permission?

2. Is it necessary to obtain consent from the child, once old enough, to continue research on collected data/samples?

3. If not able to obtain consent (i.e., not able to locate) must data/samples be destroyed?

# Can parents give permission for their children to participate in genetic research?

Suppose that when you were an infant, your parents gave their permission for a blood sample of yours to be used in research on children's health.

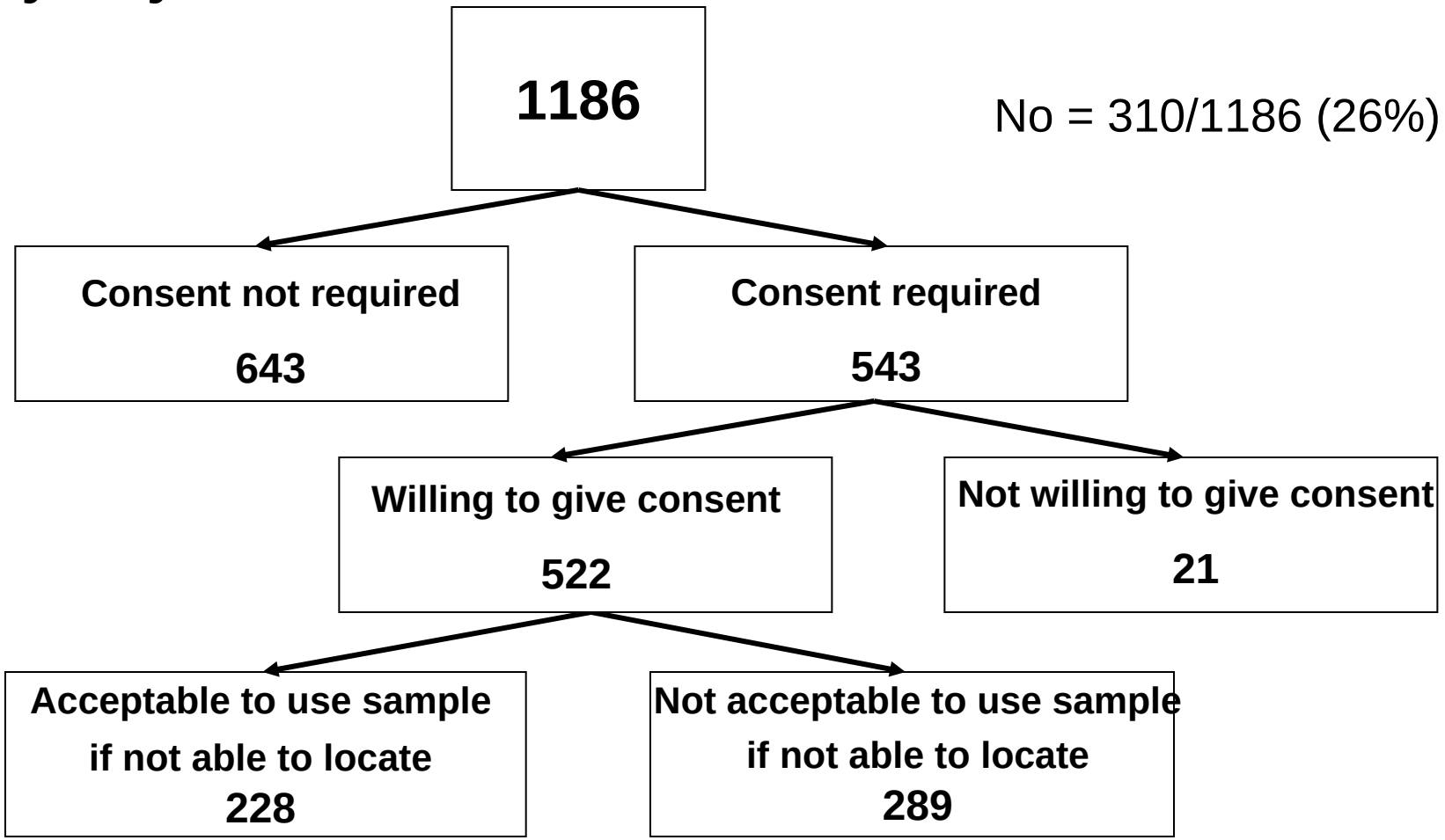
Your doctor collected samples from hundreds of infants this way.

Since then, your blood sample has been stored in a freezer along with a unique identification number and some background medical information about you.

Several decades have passed and all of the infants whose blood samples were collected are adults.

The researcher now wishes to continue to use your sample for research.

Suppose that the researcher could not locate you. Would it be acceptable to use your sample anyway?



# Is it acceptable to begin research with just parental permission?

- Presumption of parental authority for decision making about children
- IRB review of benefits and risks
  - Limitations on parental decision making
  - No more than a minor increase over minimal risk
- Public/community acceptance of the social value of conducting research with children

# Is it necessary get consent for continued use?

- What do we mean by “consent”
  - Agreeing to continued use by signing a “form”
  - Agreeing to continued use
  - Respect preferences of those who request no continued use

- Respecting preferences
  - Adequate disclosure
    - Direct conversations
    - Newsletters and websites

- Meaningful disclosure of research should be sufficient
  - Respects preferences of people who request no further use

- Unambiguous affirmative consent should not be necessary for all continued use of samples/data from children

# When is it appropriate to proceed without explicit permission in circumstances?

- Examples where we would respect explicit requests to stop?
  - Parking car in front of neighbor's house
  - Enrollment in retirement programs
  - Telemarketing do not call lists
  - Newborn screening
  - "Emergency" Research
- May be justified by the value of the action to
  - The "actor"
  - The "recipient"
  - Society

# Should we continue to use data from those who can not be contacted?

- 25% expressed concern about this approach
- What role should minority viewpoints play in research ethics policy?

# Balancing minority objections with the value of research

- Potential harms to participants and other children whether or not research continues
  - Not simply researchers' interests vs. participants' interests
  - Societal interest in further research
  - Societal interest for individuals to express objections

- Understanding the rationale of the objections
  - Psychological value of participation in decisions
  - May represent response to other social concerns

- Deliberative community engagement to address value of continuing research beyond age of consent
  - Respect for participants and communities who may have objections
  - Social value of ongoing analysis of pediatric data sets for cancer, infectious diseases, injuries etc.

# Conclusions

- There is no one single approach to the ethical issues related to genetics research

- Don’t generalize
  - to avoid over or under estimating risks of genetic information

- Tailor the approach about
  - The plan about disclosure of information
  - The consent process