Cases….

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Consent to archiving + future use – using discarded specimens

- Your institution wants to build a research resource by performing WES on surgical and pathology “waste” specimens from patients and archiving those data
- What kind of consent do they need, if any?
- Can they use an opt-out regime, rather than opt-in?
- What kind of consent is needed for future research use?
- How should they handle return of results & incidental findings?
- Should they consult the community?

Pancreatic cancer biobank + family registry

- Your institution wants to start a pancreatic cancer biobank aggregating both data and specimens for research
- They also want to start a family registry including unaffected relatives
- How should they do that? What issues need to be resolved? How?
- What approach should they take to biobank and family governance?

Preemptive pharmacogenomic testing + CDS

- Your institution would like to harness the predictive power of genomics to institute routine pharmacogenetic testing of all patients
- They would then like to communicate findings to clinicians in a way that is easily understood and actionable
- How do they do this? What issues do they need to consider? How should they resolve them?

Families initiating autism biobank with genomic + EHR data

- A group of families approach you to help design a research biobank on autism
- They want to deposit the whole genome sequence (WGS) of their affected children
- They also want to link to the full eleectronic health record of their children
- They want to make this maximally available to researchers
- What issues do they need to address? What are your recommendations?

Others

- Your cases…?

Return of Genomic Results: Challenges of Delivering Data & Results

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All opinions are those of the author, not NIH, NCI, or NHGRI.

Disclosures

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  - PCORI
  - MnDRIVE Transdisciplinary Research (UMN)
- No other relevant disclosures.

Importance of the problem

- RoR is "one of the thorniest current challenges in clinical research" --Francis Collins, *NYT* 8/25/12
- NIH has created a CSER Consortium to speed progress
- The problem is inspiring an outpouring of research & scholarship, Pres. Commission on Bioethics (2013), provision in pending NPRM to amend the Common Rule
- Data → most **research** participants want & expect return of their individual findings, but custom has been no return
- In **clinical** WGS/WES IFs (or secondary findings) "are highly likely, if not inevitable" --ACMG 2012
- This issue is a major challenge in **translational genomics from research → clinical → public health**

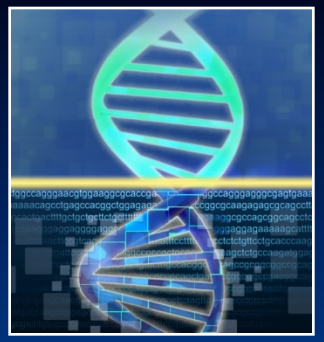
All the more important because of…

- The Precision Medicine Initiative (PMI)
- NIH, FDA, White House collaborating to developing a national research cohort of ≥ 1 M volunteers
- Participants share genomic info, biospecimens, EHR data, lifestyle & environmental exposure data
- High participant engagement & partnership, with full access to individual data, individual results & aggregate cohort results
- Robust RoR is anticipated by the PMI framework report

--NIH: www.nih.gov/precision-medicine-initiative-cohort-program

--White House: www.whitehouse.gov/precision-medicine

Overview



- Research routinely generates IFs/IRRs of clinical, reproductive, or personal importance
- Dealing with this challenges the clinical/research dichotomy that has structured bioethics & health law
- It also challenges past approaches to biobank research
- Emerging consensus suggests that researchers and biobanks have duties to return some IFs/IRRs
- Recommendations for IFs in clinical genomics and now public health genomics are emerging
- RoR is a translational problem, requiring new models of translational science to harvest benefit across research, clinical care & public health

Our work on these problems

Consortium on Law and Values in Health, Environment & the Life Sciences

- "Managing Incidental Findings in Human Subjects Research" NIH/NHGRI #1-R01-HG003178 (Wolf, PI)
- "Managing Incidental Findings and Research Results in Genomic Biobanks & Archives" NIH/NHGRI #2-R01-HG003178 (Wolf, PI)
- NHLBI workshop on IFs/IRRs in genetics; in Fabsitz et al. (2010)
- "Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment" NIH/NCI/NHGRI #R01-CA154517 (Petersen, Koenig, Wolf, PIs)
- Brocher Centre Workshop in Switzerland, Nov. 2013 (w/Kaye, Elger)
- Robert Wood Johnson Foundation Investigator Award (Wolf, PI)

National Human Genome Research Institute

National Cancer Institute

National Heart Lung and Blood Institute

Robert Wood Johnson Foundation

Fondation Brocher

cser Clinical Sequencing Exploratory Research

Return of Results & IFs in Research Genomics

Definitions

- **Incidental Finding** (IF): "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of research but is beyond the aims of the study"

- **Individual Research Result** (IRR): a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of research on the focal variables under study in meeting the study's aims

- **Aggregate Research Results**: findings concerning the research population (usually published) that are discovered in the course of research on the focal variables under study in meeting the study's aims

(SM Wolf et al., *Journal of Law, Medicine & Ethics* 2008;36(2):219-48)

Clinical Sequencing Exploratory Research

*Moving the **Genome** Into the **Clinic***

377 Researchers
21 Institutions
1 Consortium

RC Green et al. The Clinical Sequencing Exploratory Research Consortium: Accelerating the evidence-based practice of genomic medicine. *Am J Hum Genet* 2016.

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www.cser-consortium.org

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		% participants with ≥ 1 finding *re* phenotype (median # of variants reported)			
Clinical Characteristics	**Sample Size**	**Pathogenic or Likely P**	**VUS**	**Single* Recessive**	**Other**
Cancer (all)	1142	6.2%(1)	36% (1)	2.4% (1)	0.4% (1)
DD/ID					
Syndromic ID/Autism	431	19% (1)	13% (1)	0.7% (1)	1.2% (2)
Other	50	28% (1)	28% (2)	14% (1)	0%
Cardiovascular					
Cardiomyopathy	104	27% (1)	28% (1)	0%	1.0% (1)
Other	274	5% (1)	11% (2)	0%	0.4% (1)
Ophthalmology	80	39% (1)	16% (1)	7.5% (1)	0%
All Other Characteristics	137	18% (1)	28% (1)	19% (1.5)	2.2% (1)

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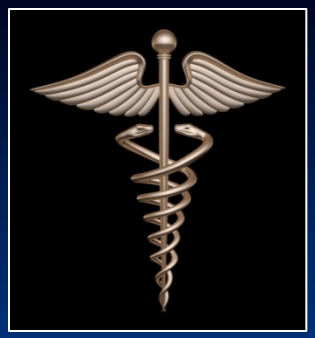
Category	Sample Size	Number (%) of participants with ≥1 finding	Range (sites)
ACMG Incidental Findings: Pathogenic	3296	49 (1%)	0 – 19
ACMG Incidental Findings: Likely Pathogenic	2622	19 (1%)	0 – 6
Non-ACMG Incidental Findings: Pathogenic	2310	59 (3%)	0 – 18
Non-ACMG Incidental Findings: Likely Pathogenic	1924	24 (1%)	0 – 5
PGx Genes: FDA Indication	1008	359 (36%)	0 – 191
PGx Genes: Other	799	70 (9%)	0 – 49
Carrier Genes: Pathogenic	2052	660 (32%)	0 – 274
Carrier Genes: Likely Pathogenic	1841	245 (13%)	0 – 108
Tumor: Potentially Clinically Relevant	756	444 (59%)	0 - 246

How should we handle these findings?

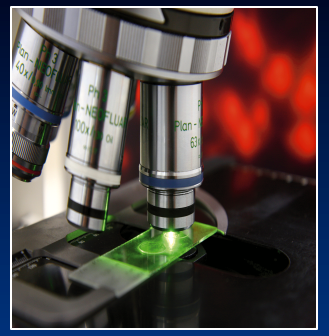
- What criteria define returnable IFs/IRRs? Do these include IFs/IRRs of reproductive significance? Personal significance?
- Do researchers have a duty to hunt in their data?
- What should researchers do once they spot a suspected IF/IRR? Evaluate how? Seek a consult? What's the pathway?
- What should be disclosed to the research participant or participant's physician and how? Should family have access?
- How do you plan for this? What should research protocols & consent forms say about managing IFs/IRRs? What should IRBs & funders require?
- What should biobanks & data archives do?

Why is this problem hard? IFs & IRRs bridge research & clinical care

- IFs & IRRs are discovered in the course of research, but have clinical, reproductive, and personal implications
- IFs include findings routinely communicated in clinical care
- IRRs are findings generated in pursuit of research aims, but recommendations urge returning the subset with analytic validity, clinical utility, and high health significance
- The problem of IFs & IRRs thus challenges the foundational dichotomy between research & clinical care (Wolf 2010)
- This is a problem in translational science….



U.S. health law/bioethics—built on a traditional dichotomy



Doctor-patient

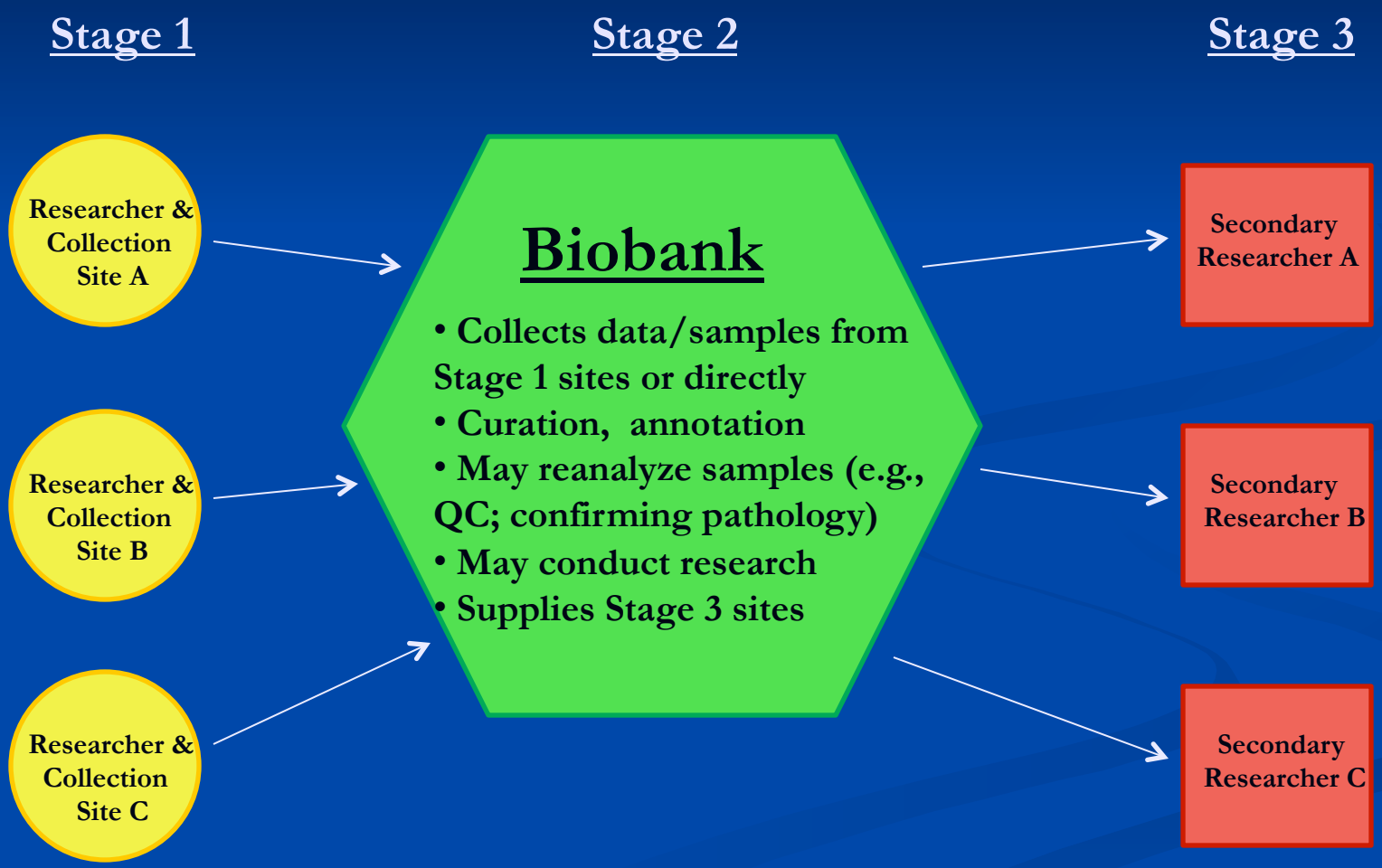
- MD owes duty of clinical care
- Duty is to serve pt.'s interests
- Patient can sue for damages
- Retrospective adjudication of fault & liability
- Governed by state tort and contract law
- Guided by ethics codes
- Info disclosed: professional standard of care & info material to patient choice, values

Researcher-participant

- Researcher owes little clinical care
- Duty is to seek generalized knowledge
- Participant generally can't sue under research regs; use tort law
- Prospective screening of proposed protocols by IRBs
- Governed by federal regs. on human research (Common Rule, FDA regs.)
- No ethics codes until Nuremberg
- Info returned: ??

IFs/IRRs challenge biobank models too….

Biobank Research System (from Wolf et al. 2012)



Project recommendations on IFs/IRRs:

(Wolf et al. *JLME* 2008, *Genet Med* 2012)

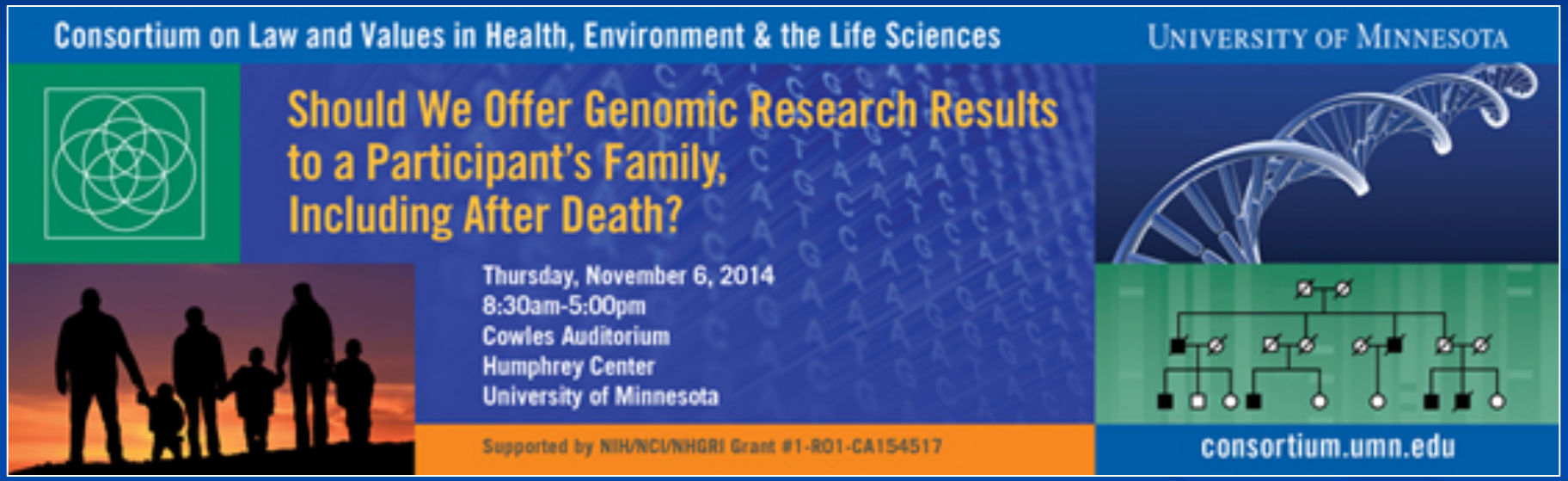
- Researchers do shoulder duties to manage IFs/IRRs
- Researchers should address duties in advance—in protocol & in consent process; get IRB approval

❖ **Should return** IFs/IRRs that:
- are analytically valid & in compliance with law (e.g., CLIA)
- reveal established & substantial risk of a serious health condition
- are actionable (significant potential to alter onset, course, or tx)
- **if** return is consented to by participant (at initial consent or after)

❖ **May return** additional IFs/IRRs if:
- they reveal established & substantial risk of likely health or reproductive importance, or personal utility

❖ Biobank research systems should clarify criteria, analyze findings, reidentify, recontact individuals

New issue -- Family access, including after death of the participant



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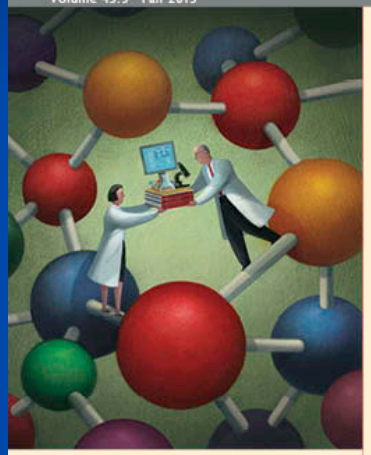

SYMPOSIUM

Should We Offer Genomic Research Results to a Participant's Family, Including After the Participant's Death?

GUEST EDITED BY Susan M. Wolf, Barbara A. Koenig, and Gloria M. Petersen

Plus more inside...

INDEPENDENT ARTICLES

Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations

Susan M. Wolf, Rebecca Branum, Barbara A. Koenig, Gloria M. Petersen, Susan A. Berry, Laura M. Beskow, Mary B. Daly, Conrad V. Fernandez, Robert C. Green, Bonnie S. LeRoy, Noralane M. Lindor, P. Pearl O'Rourke, Carmen Radecki Breitkopf, Mark A. Rothstein, Brian Van Ness, and Benjamin S. Wilfond*

*Note: Authors are listed alphabetically after the 3-person investigator team and Research Associate.

Introduction

The debate about how to manage individual research results and incidental findings in genetic and genomic research has focused primarily on what information, if any, to offer back to research participants.[1] However, increasing controversy surrounds the question of whether researchers have any responsibility to offer a participant's results (defined here to include both individual research results and incidental findings) to the participant's relatives, including after the participant's death.[2] This question arises in multiple contexts, including when researchers discover a result with potentially important health implications for genetic relatives, when a participant's relatives ask a researcher whether any research results about the participant have implications for their own health or reproductive planning, when a participant's relative asks whether any of the participant's results have implications for a child's health, and when the participant is deceased and the participant's relatives seek information about the participant's genetic results in order to address their own health or reproductive concerns.

The question of whether relatives (a term used here to include genetic relatives as well as family members, such as spouses or partners, without a genetic relationship to the participant — see Definitions box) should be offered any of the participant's research results (whether at the relative's request or in an offer initiated by investigators) is challenging. Ethical and legal approaches to informed consent, research protections, and privacy safeguards in the United States mainly focus on the rights and interests of individual participants. However, first-degree biological relatives have 50% of their genetic material in common (with more distant relatives sharing genetic material to a lesser degree), and other close relatives may be co-parenting the participant's child or sharing other family caregiving. A research participant's genomic results may thus have relevance for others. For genes with known pathogenic variants whose pattern of inheritance is understood, researchers may face the question of whether to encourage the participant to share results with relatives or whether the investigators themselves should seek to share the results, including after the research participant's death. Sharing through either route may allow relatives to seek genetic counseling and consider genetic testing, for themselves or children.

We consider return of the participant's genomic results to relatives in the research context. This is an emerging issue facing researchers. In contrast, clinicians have long faced questions of whether to alert relatives to a heritable condition or pathogenic variant

Consensus recommendations--overview

- Ask participant's preferences on sharing w/family, including after death; designation of personal representative
- Research context supports passive disclosure policy
  - Research vs. clinical care; research burden
  - Family already has some access; PR can offer access
- Researchers should support PR decision-making, considering decedent's preferences
- Exceptional circumstances may warrant considering active offer (variant is highly pathogenic & actionable, relative is likely to have variant, sharing is likely to avert harm)
  - Address case x case

(SM Wolf et al. Returning a research participant's genomic results to relatives: Analysis & recommendations. *J Law Med Ethics* 2015;43:440-63.)

All of that is in the context of research…

- **Clinical** integration of genomics is under way
- What should the approach be to RoR in clinical genomics?

Return of Results & IFs in Clinical Genomics

What should the standards for return be?

- Berg et al.—Deploying clinical WGS & using "bins" (2011):
  - **Clinicians should return Bin 1 results:**
    - "medically actionable"
    - "direct clinical utility based on the current medical literature"
    - "known to cause disease or strongly predicted to disrupt function"
  - **Clinicians may return Bin 2 results:**
    - "clinically valid but not directly actionable"
    - some patients may wish this information
    - Bin 2A—low risk, doubtful current utility
    - Bin 2B—medium risk but incomplete penetrance, doubtful utility, may cause distress (includes carrier state of reproductive signif.)
    - Bin 2C—may cause high distress
  - **Clinicians should not return Bin 3 results:**
    - variants of no or unknown clinical significance (VUSs) ←

Am Coll Med Genetics & Genomics (ACMG): 2012 approach in clinical WGS/WES

ACMG Policy Statement (2012):

- IFs "are highly likely, if not inevitable" in WGS/WES
- labs & clinics need policies on disclosure of IFs
  - share policy with patients
- Before testing, counsel individuals on what "will or will not be disclosed"
- **Allow patients to opt-out** of receiving some IFs, tho' "exceptional" cases may arise

ACMG 2013 approach in clinical WGS/WES:

- Specifies "minimum list" of 56 addt'l genes that labs should analyze when sequencing for another indication (specific cancers, cardiovascular conditions, Malignant hyperthermia)
  - No consent sought from patient to analyze these specific genes
  - Patient who does not want IFs must decline sequencing altogether
- Labs should ascertain gene variants of:
  - known or expected pathogenicity, high penetrance, actionability
  - Lab **must** report these to clinician
- Clinician shares these with patient
  - "**did not favor offering the patient a preference** as to whether or not to receive the minimum list of " IFs
  - "this may be seen to violate existing ethical norms regarding the patient's autonomy and 'right not to know' genetic risk information."
- Constitutes **opportunistic screening**

Debate in *Science*
(published May 2013)

Sciencexpress

Patient Autonomy and Incidental Findings in Clinical Genomics

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Returning genetic incidental findings without patient consent is misguided.

Sciencexpress

Ethics and Genomic Incidental Findings

Amy L. McGuire,[1*] Steven Joffe,[2*] Barbara A. Koenig,[3] Barbara B. Biesecker,[4] Laurence B. McCullough,[1] Jennifer S. Blumenthal-Barby,[1] Timothy Caulfield,[5] Sharon F. Terry,[6] Robert C. Green[7†]

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†Although some of us (A.L.M., R.C.G.) were members of the ACMG Working Group that wrote the recommendations, this paper does not represent the official views of the Working Group or the ACMG.

Laboratories have an obligation to report clinically beneficial incidental findings.

ACMG amendment—April 1, 2014

- ACMG Board updates its policy--allows patients to **opt out of additional IFs analysis**
- "consensus among ACMG members that patients should have an opportunity to **opt out** of the analysis of medically actionable genes when undergoing whole exome or genome sequencing."
- "ACMG Board…has voted to recommend that…an 'opt out' option be offered to patients"
- Still unresolved:
  - Can patients elect analysis of some extra genes but not others?

ACMG 2013 on children:

- Long-standing consensus (ASHG/ACMG/AAP) restricts genetic testing in minors to that medically needed
- Waiting to test for adult-onset conditions protects the child's autonomy by allowing the child to decide at adulthood
- AAP/ACMG 2013: child's best interests should govern

But--

- ACMG 2013 urges ascertaining & reporting even variants for adult-onset conditions regardless of patient's age
- Argues the returning variants for adult-onset conditions can alert parents to their genetic risks; parent health=in child's BI

Remaining debate--

- Does that subordinate the child's separate autonomy?
- Should parents be counseled on option to wait, allowing child to decide on testing later?

Return of Results & IFs in Public Health Genomics

Return of IFs in genetic screening

- Lewis & Goldenberg argue for RoR from research conducted with newborn screening (NBS) dried blood spots (DBS)
- Cases brought suing for failure to return results from pilot testing (eg, *Ande v. Fost* (Wisc. Ct. App. 2002); *Dinkins v. Hutzel Hosp.* (6th Cir. 1996))
- Some state statutes (eg, S. Ca.) explicitly allowing return of results from research conducted with DBS
- Public programs w/public duties
- (MH Lewis, AJ Goldenberg. Return of results from research using newborn screening dried blood samples. *JLME* 2015)

Return of results in public health research

- Natl Health & Nutrition Examination Survey (NHANES)—NAS workshop 2014 on RoR
- Mission: "participant health assessment and biobanking for research"
- Already returning many results; Q is whether to include genetic results
- Public duties to responsibly handle results

(Issues in returning individual results from genome research using population-based banked specimens, with a focus on the National Health and Nutrition Examination Survey. Nat'l Research Council 2014)

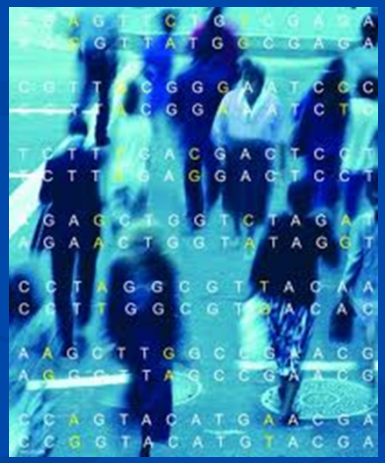
Return of environmental exposure results

- NAS, Human Biomonitoring for Environmental Chemicals, 2006: "subjects should be told (or offered the chance to be told) whatever researchers know (or do not know)"
- EPA, Scientific and Ethical Approaches for Observational Exposure Studies, 2008: "Researchers need to develop the approach for reporting results to the participants, community, stakeholders, media, and others…[in] planning of the study."
- Nat' Conversation Leadership Council, National Conversation on Public Health and Chemical Exposures, 2011: Recomm. 5.5: "Increase public access to data by… ensuring that respondents have access to data collected on them…

(JG Brody et al. Reporting individual results for biomonitoring and

Vision of public health genomics

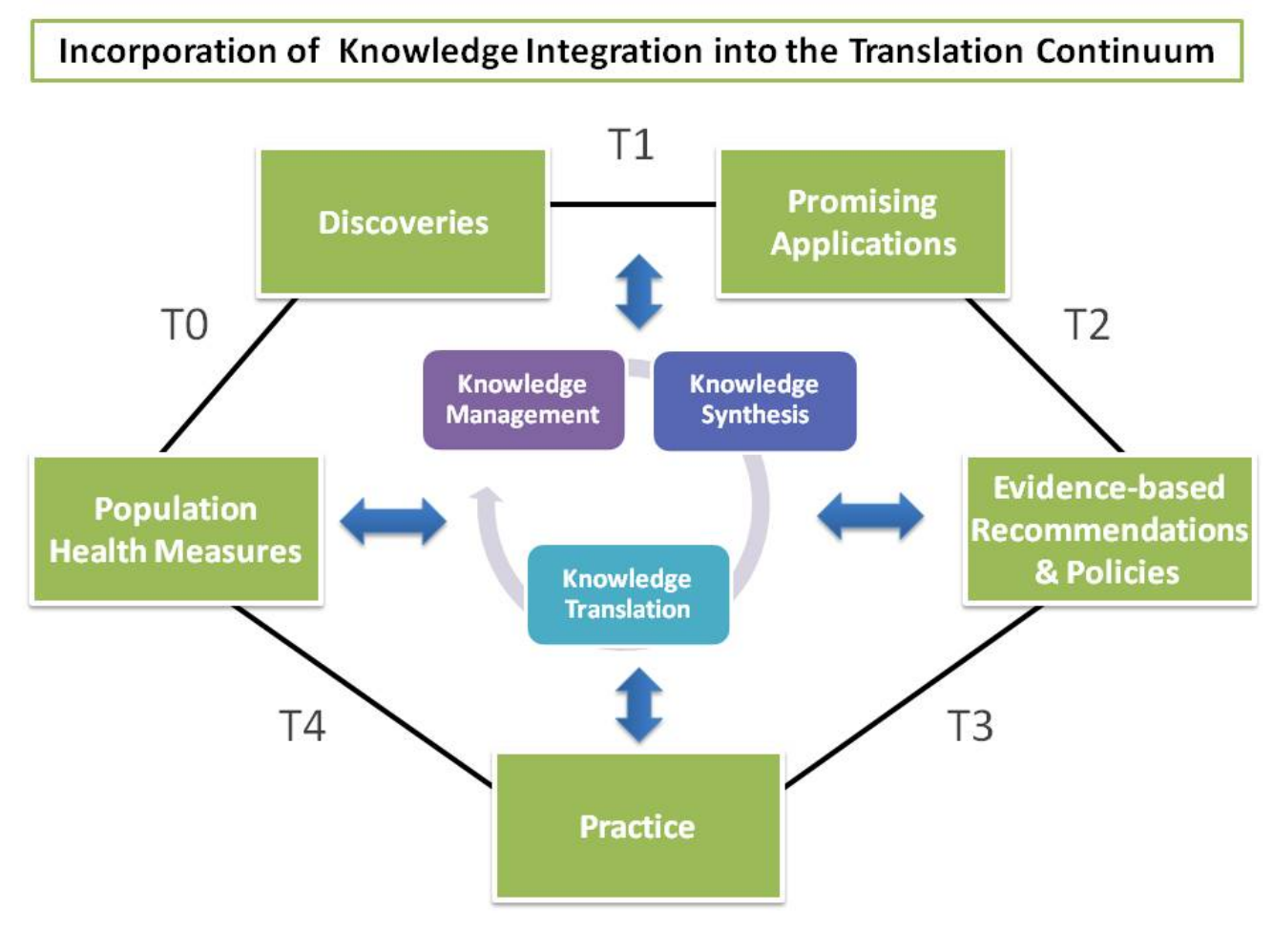
- Determining when genetic/genomic tests are ready for screening application (EGAPP)
- Distinguishing role of genes vs. environment in health → "precision public health"
- Targeting prevention efforts
- Genomics of pathogens & host
- Modernizing surveillance (big data)



(MJ Khoury et al. Precision public health for the era of precision medicine. *AJPM* 2015)

Return of Results Across the Translational Spectrum: Research→Clinical→Public Health

Models of translational genomics



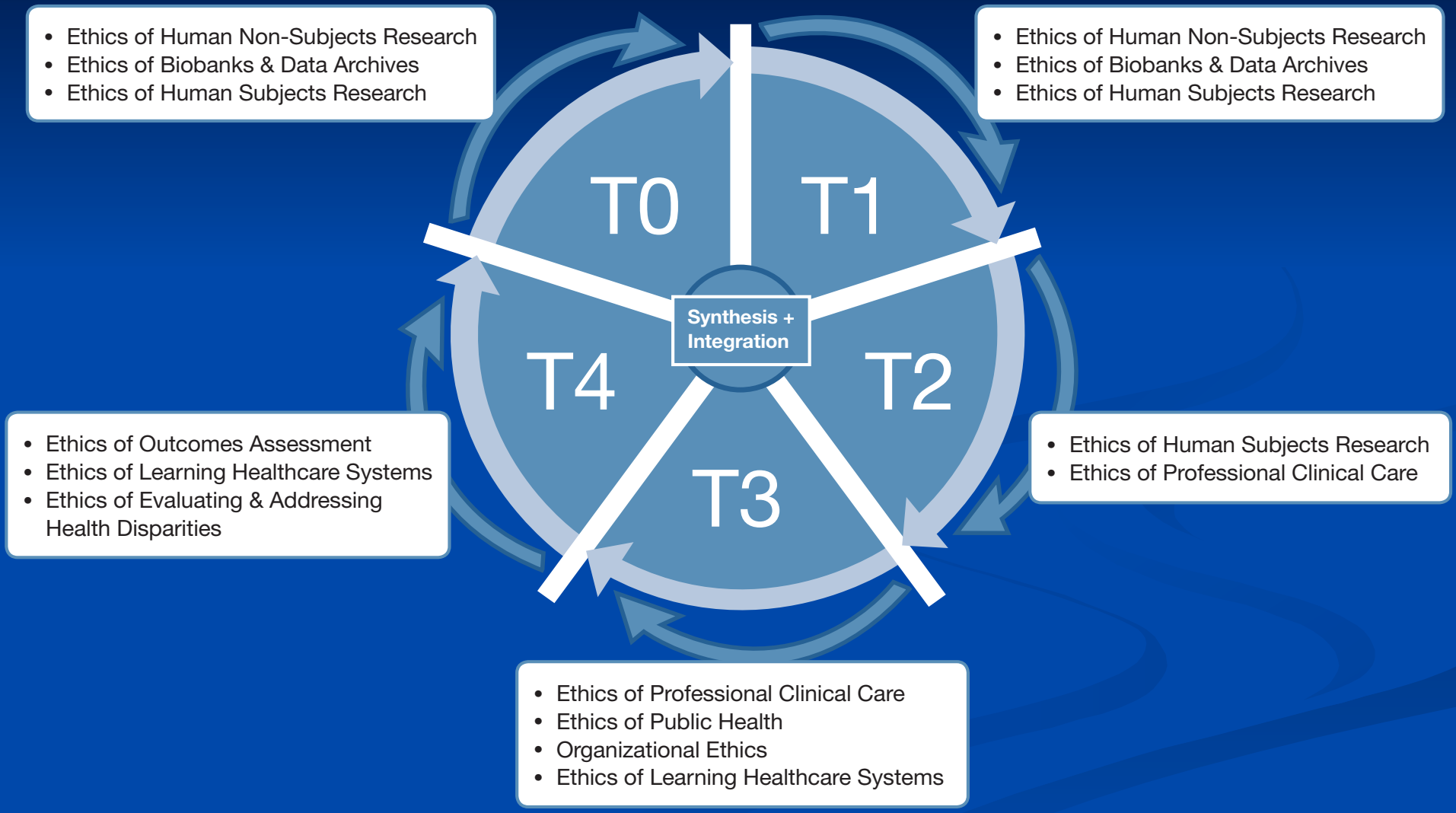
NCI Cancer Epidemiology Matters Blog. Image adapted from **MJ Khoury** et al. Knowledge integration at the center of genomic medicine. *Genet Med* 2012;14:643-47. (Image used with permission from Nature Publishing Group.)

The challenge

- Developing the ethics of translational science
- Developing the law of translational science
- Developing best practices for translational science
  - What kind of consent?
  - Requires use of a CLIA-certified lab?
  - Record results in research or medical record?
  - Return what results & incidental findings?

(SM Wolf, B Koenig, W Burke. Mapping the ethics of translational genomics: Situating return of results and navigating the research-clinical divide. *J Law Med Ethics* 2015;43:486-501.)

Figure 1. The translational research process, framed by the ethical domains most relevant to each stage.



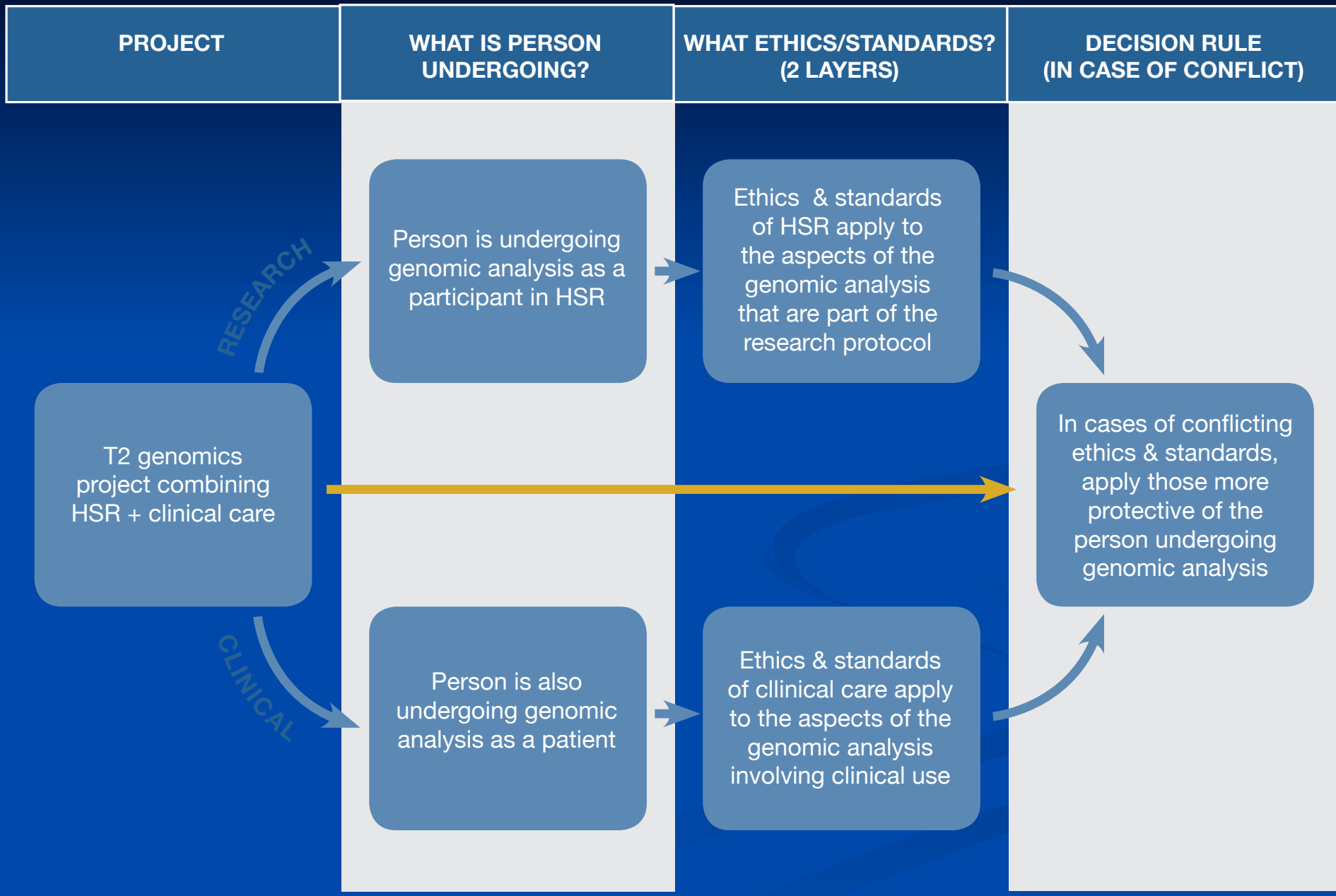
Role of RoR -- the leading edge

- Recognizing some research results as sufficiently validated, pathogenic, and actionable to be offered to participants allows investigators to pioneer practices for clinical use
- RoR can thus power the leading edge of a process expected to grow into clinical genomics best practices
- With satisfaction of screening criteria, may move into public health use
- RoR creates a translational pathway based on evidence

Translational genomics projects bridge research and clinical care

- CSER projects are largely translational genomics projects to develop evidence-based best practices for integrating genomics into clinical care
- The traditional research/clinical divide would absolve investigators of clinical duties and allow more latitude in choosing what to return, but translational genomics projects straddle research & clinical care
- Where both research & clinical standards arguably apply, use those more protective of participant welfare, choice, and rights

(SM Wolf, B Koenig, W Burke. *JLME* 2015)


PROJECT
WHAT IS PERSON UNDERGOING?
WHAT ETHICS/STANDARDS? (2 LAYERS)
DECISION RULE (IN CASE OF CONFLICT)
T2 genomics project combining HSR + clinical care
RESEARCH
CLINICAL
Person is undergoing genomic analysis as a participant in HSR
Person is also undergoing genomic analysis as a patient
Ethics & standards of HSR apply to the aspects of the genomic analysis that are part of the research protocol
Ethics & standards of cllinical care apply to the aspects of the genomic analysis involving clinical use
In cases of conflicting ethics & standards, apply those more protective of the person undergoing genomic analysis

The legal challenges

Conclusion

- Problem of return of results & IFs cuts across research, biobanking, clinical care & public health screening.
- Return of **research** IFs/IRRs is a bridge problem, challenging the architecture of health law & bioethics.
- Return of IFs/IRRs in **biobank** research requires innovation in BB research systems.
- **Clinical** integration of WGS/WES has led to controversy over the future of patient choice in clinical genomics.
- Return of results is emerging in **public health** programs.
- The problem demands a **translational** framework.
- **The core challenge across domains:** advance science & biomedicine + respect needs & choices of research participants, specimen sources, patients & public.

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  - Frances Lawrenz, PhD (UMN)
  - Working group members
- Project Manager at UMN:
  - Audrey Boyle

- **NIH, NCI/NHGRI #1R01-CA154517**
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- **NIH, NHGRI #1R01-HG008605**
- All opinions are those of the author, not the funders.

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Precision Medicine: Ethical & Legal Challenges

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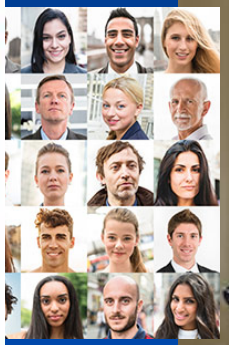
PMI challenges…

- The **Precision Medicine Initiative**
- Includes $ to NIH to develop a nat'l research cohort ≥ 1 M; each person shares genomic info, specimens, EHR data, lifestyle and environmental data
- Goals: intensified PM in cancer; develop new research models prioritizing participant engagement & privacy; advance pharmacogenomics; pioneer PM for more diseases
- **Challenges -- including return of data, interpreted results, and aggregate cohort results -- are significant**

(NIH, Precision Med. Initiative, http://www.nih.gov/precisionmedicine/)

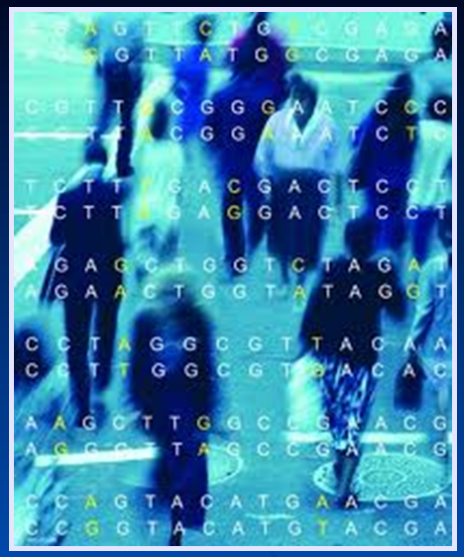
Precision Medicine Initiative



Images courtesy of NIH

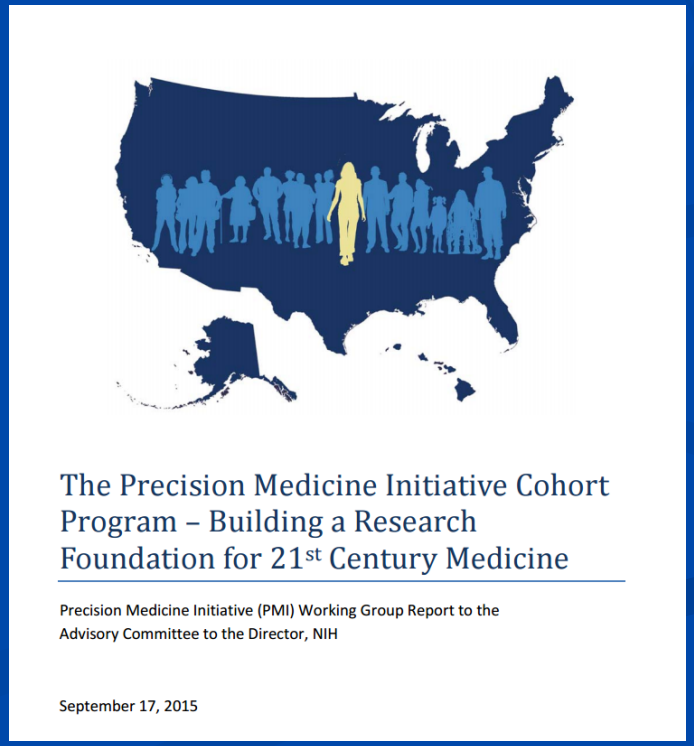
NIH Precision Medicine Initiative

Overview



- Review PMI Working Group 9/15 plan
- Identify key parameters of the PMI
- Isolate key design, ethical & legal challenges
- Propose solutions
- Isolate nagging Qs
- Identify options for addressing those Qs

PMI Working Group Plan



PMI cohort

- Recommendation 3.1: The PMI cohort should assemble one million or more individuals who agree to share their longitudinal health data and biospecimens for research and to be recontactable.
- Rec. 3.2: The PMI cohort should broadly reflect the diversity of the U.S.
- Rec. 3.3: All individuals living in the U.S. should be able to volunteer for the PMI cohort.

Recruitment

- Rec. 3.4: The PMI-CP should adopt two distinct recruitment approaches that leverage the strengths of healthcare provider organizations…, as well as the enthusiasm of individuals who wish to volunteer directly.
- Rec. 3.5: Healthcare provider organizations…must be able to consent volunteers to the PMI cohort, to share participants' electronic health record data, and to collect new biospecimens. HPOs that capture more comprehensive health care data that have a record of longitudinal follow-up of participants, that serve the diversity goals of the PMI cohort, and that can contribute significantly to the size of the PMI cohort should be preferred.

Data sharing & recruitment

- Rec. 3.6: The PMI -CP should share PMI cohort-generated research data with participating HPOs that are providing ongoing data and biospecimens to the PMI cohort, according to participant preferences.
- Rec. 3.7: The PMI-CP should seek to recruit individuals rapidly…to an initial goal of one million or more participants, and continue to accrue participants throughout the lifespan of the PMI-CP.

Participant engagement

- Rec. 4.1: Research participants and their advocates should be central partners in the governance, design, conduct, oversight, dissemination, and evaluation activities of the PMI-CP.
- Rec. 4.2: The PMI-CP must prioritize building and maintaining trust with participants and communities by operationalizing the best approaches for participant engagement and scientific integrity.
- Rec. 4.3: Engagement and communications with participants should be managed through a single entity….

Communication with participants

- Rec. 4.4: The PMI-CP's approach to communication with potential participants, enrolled participants, and the public should utilize multiple technologies, including internet, telephone, and mobile-based communications….
- Rec. 4.5: A standardized and centralized electronic consent protocol should be used across all PMI cohort participants to…minimize organizational burden, and maximize participant recruitment.
- Rec. 4.6: Participants should be able to set preferences for invitations to participate in supplementary or complementary studies that are outside the general PMI-CP protocol.

Return of results

- Rec. 4.7: The PMI-CP should ensure the responsible return of personal results and information to individual participants and sharing of aggregate findings from its investigations with participants so all volunteers may have opportunity to benefit from the science.
- Rec. 4.8: A Return of Results and Information Subcommittee that includes substantial representation from the participant community should be established to oversee the development and implementation of policies related to the return of aggregate and individual results to participants.

Data types

- Rec. 5.1: Guided by the scientific use cases and consideration of value to participants, the PMI-CP should anticipate and collect a diverse set of data types, beginning with a more limited set of high-value variables to be acquired primarily at entry from all PMI cohort participants, but also including a limited set of longitudinal variables….
- Rec. 5.2: A Data Subcommittee should be formed to consider and evaluate core data elements.

EHR data

- Rec. 5.4: The PMI-CP should develop standardized and, to the extent possible, automated mechanisms to acquire clinical data efficiently from participating HPOs.
- Rec. 5.5: The PMI-CP should develop and implement a rigorous data curation program for the core datasets to create analysis-ready datasets for a broad range of uses.
- Rec. 5.6: The PMI-CP should periodically implement and revise phenotype algorithms for a number of core diseases and outcomes of interest….

EHR data (cont'd)

- Rec. 5.8: The PMI-CP should support development and adoption of automated text analytics that can be used both centrally and locally to extract for research purposes the information contained in narrative clinical documents.
- Rec. 5.9: The CC should interface with the CMS and other insurers to retrieve medical claims data for integration with participant EHR data.

Participant-centered technologies

- Rec. 5.10: The PMI-CP should support development and evaluation of tools that enable individuals to acquire, transmit, and continuously update their EHR data to the PMI cohort from multiple provider organizations.
- Rec. 5.11: The PMI-CP should support development of tools for individual participants to review, annotate, and contextualize the clinical data provided by them. Annotations and revisions of clinical data will be for the purposes of PMI cohort and research use, not clinical care.

Genomics & specialized lab data

- Rec. 5.12: Biomolecular data should be acquired and maintained permanently, with attention to including metadata that describes the methods and technologies used to produce it.
- Rec. 5.13: The PMI-CP should generate a core set of biologic data at scale for the PMI cohort, such as specific analytes and broad genomic data, as soon as it is feasible to do so.

Data set & evolution

- Rec. 5.14: The PMI-CP should employ probabilistic record linkage strategies, including privacy-preserving methods for sensitive information.
- Rec. 5.15: The PMI-CP should seek to align its core data set with existing large-scale biobanks where possible…. [T]he recommended initial core data set includes data from EHRs, health insurance organizations, participant surveys, PMI baseline health exams, mHealth technologies, and biologic investigations….

Biobanking

- Rec. 6.2: Before participant recruitment, the PMI-CP should establish a full service, central biobank that manages all aspects of collection, processing, storage, retrieval, sample tracking, and biochemical analysis. The capacity of this facility should be for at least several million specimens and utilize state-of-the-art robotic processing and storage systems to facilitate high-volume acquisition and retrieval.
- Rec. 6.3: Only new specimens should be collected for the PMI cohort and banked.

Specimen collection & storage

- Rec. 6.4: Specimens should be collected, shipped, processed, and stored using CLIA procedures.
- Rec. 6.5: The PMI-CP should collect blood and other samples that anticipate current and future uses for baseline samples and samples collected at subsequent intervals. These include serum and plasma to support analysis of routine and advanced analytes (e.g. metabolites, cell-free DNA), leukocyte nucleic acids, blood cells stored to permit future sorting and analysis, samples for potential exposure studies (e.g. hair, nails), and samples for potential microbiome studies.

Inclusion

- Rec. 7.2: NIH should carefully examine issues related to inclusion of three special populations: children, decisionally impaired individuals, and PMI cohort participants who become incarcerated after enrollment. NIH should develop specific approaches to address the needs of these individuals so that they may be included and retained in the cohort.
- Rec. 7.3: The PMI-CP should anticipate the need for special provisions to allow for continued engagement and follow up with participants who have undergone life events or other changes that alter their participation status or capacity.

IRB

- Rec. 7.4: The PMI-CP should have a single IRB (to the extent permitted by law)…to ensure prompt and thoughtful consideration of the evolving protocols in the PMI cohort and the central importance of participants as research partners. NIH should consider whether such an IRB would best be located at the NIH or at the CC.
- Rec. 7.6: The PMI-CP IRB should include a substantial number of members of the public and representatives of the participant community.

Common Rule revision

- Rec. 7.7: The PMI-CP should support revisions to the Common Rule that enable use of broad consent for secondary use of data and specimens to allow knowing, willing participation and facilitate research.

Privacy & security

- Rec. 7.8: To safeguard against unintended release of the information, NIH should seek to establish an exemption under [FOIA] for release of genomic and other data held by the federal government.
- Rec. 7.9: Unauthorized re-identification or recontacting of participants should be expressly prohibited in agreements for the use of specimens and data, and NIH should pursue legislation penalizing such actions.
- Rec. 7.10-.11: The PMI-CP should only enter into agreements with sensor technology developers…[with] security and privacy measures…to safeguard device users' data….[and] that agree not to sell or use information generated….

Confidentiality

- Rec. 7.12: To protect individual PMI cohort data from disclosure in civil, criminal, administrative, legislative, or other proceedings NIH should require all users of identifiable data to secure a certificate of confidentiality from NIH…. NIH should seek legislation to strengthen Certificates of Confidentiality to ensure that disclosure by researchers is not optional, other than with consent or for certain public health exceptions. This will be critical to ensure that data on PMI cohort participants is not used for any purpose other than research.

Anti-discrimination

- Rec. 7.13: NIH should encourage…an Executive Order to ensure that research information…is not used by any executive agency to deny federal benefits.
- Rec. 7.14: Participants should be informed that some uses of their genetic information are prohibited by [GINA], and informed of the limitations of the Act's protections.
- Rec. 7.15: Participants should be notified promptly… following discovery of a breach of privacy. Notification should include…the types of information involved in the breach, steps individuals should take to protect themselves from potential harm, if any, and steps being taken to investigate the breach and mitigate losses.

Patient access to data & results

- Rec. 7.17: …NIH should support ongoing Administration and private sector efforts to promote patient access to their health records, the exchange of health information across providers, and broad system interoperability of electronic health records.
- Rec. 7.18: The PMI-CP should only enter into agreements with sensor technology developers that have policies in place that allow individuals a right of access to their sensor device data and allows them to contribute it to the PMI….
- Rec. 7.19: The PMI-CP should only enter into agreements with sensor technology developers that will provide access for participants to, and interpretations of, sensor device data, including environmental data.

"Collateral participants"

- Rec. 7.22: The PMI-CP should conduct or support research to understand participants' preferences. These evaluations will help to elucidate any additional policy gaps….
  - If families are recruited, consider how to maintain autonomy of individual family members, for example, if remote monitors are used in the home.
  - Consider how to protect the privacy and autonomy of "collateral participants" in addition to family members… through the unintentional collection of identifiable information of non-participants.

Governance & oversight

- Rec. 8.4: Cross-agency coordination is essential and should continue to be a component of the governance structure.
- Rec. 8.5: Final oversight authority for the cohort should reside with the NIH Director.

Discussion & questions