Ethical Issues in Genetic Testing

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Conflicts of interest

- I have been a PI or sub-I for:
  - Allergan, Celgene, Leo Pharma, Galderma, Novartis
- I will not be making therapeutic recommendations during this presentation
- I work at the VA, and am not speaking on their behalf

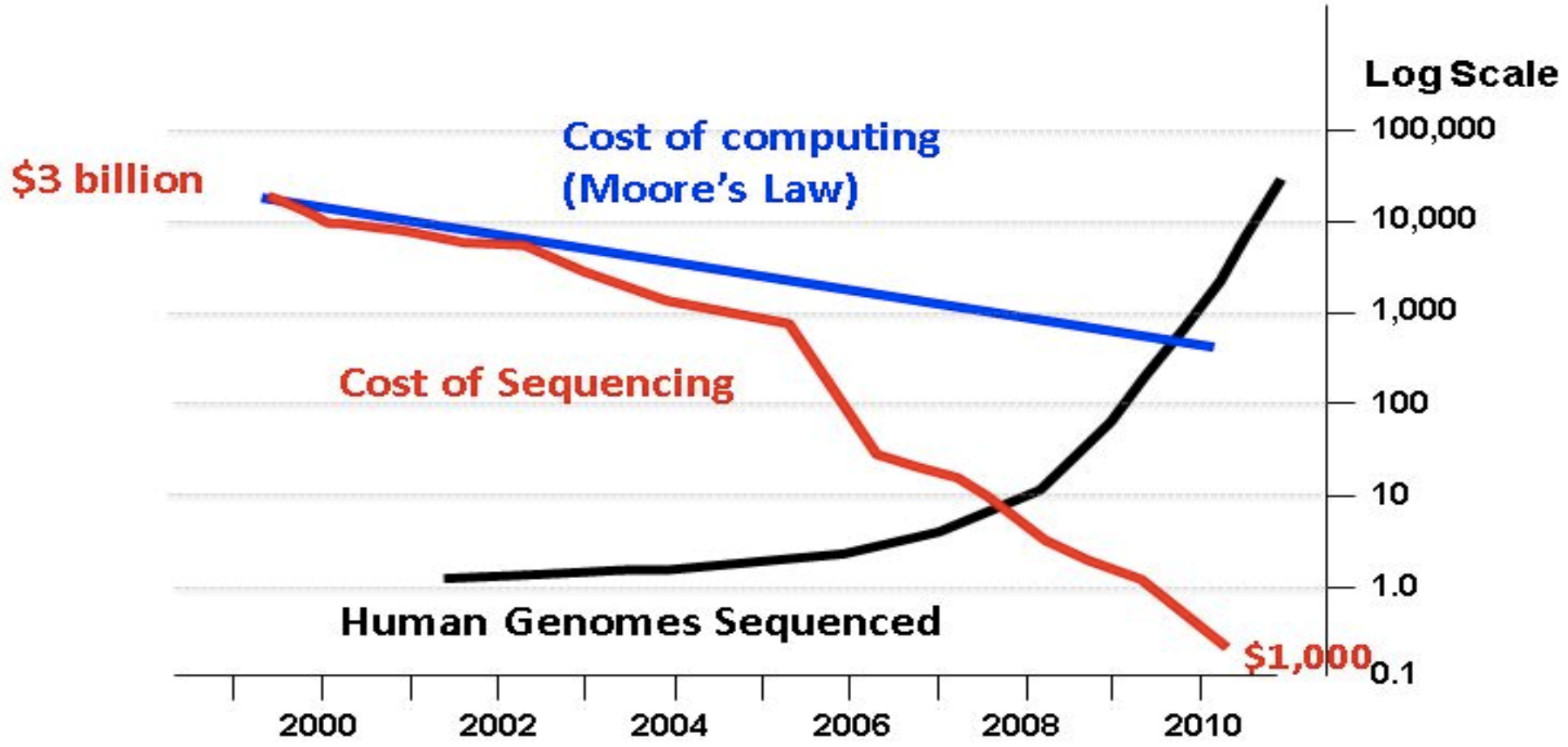
- Genetic information
  - genetic testing for patients and/or family members up to 4th degree relatives
- Genetic test
  - any analysis to detect genotypes, genetic mutations, or chromosomal changes
- Whole genome sequencing (WGS)
  - Complete DNA sequence of an organism at 1 time
- Whole Exome sequencing (WES)
  - Sequencing of only the DNA that codes for proteins

Outline

- Introduction to Genetic Data ethics
- Changes to the Common Rule
- Ethical issues surrounding Biobanks
- Reporting Incidental Findings
- Special issues in Pediatric populations
- Bedside genetic testing in dermatology

Adapted from The Economist

The Sequencing Explosion



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Do genetic data raise unique ethical issues?

Yes

- Potential increased accuracy of prediction in pre-disease state
- Ability to confirm or deny family relations
- Additional issue of direct implications for family members
    - Possible Duty to Warn
- May create an unexpected identity threat
- Stability of DNA in stored materials
    - Can be obtained from small amount of material, potentially without consent

No

- Informed consent, confidentiality and protection of sensitive data pertain to all aspects of medicine
- Risks of genetic exceptionalism
- Effect of illness on family dynamics is important for all of medicine
- Individual scenarios should be addressed but effect may not be universalized

Genetic Data ethics may require more attention to how and why the data are being obtained.

Reasons for genetic testing

- Diagnostic testing
  - Symptoms already manifest, focused
- Carrier testing
  - Unaffected, but children at risk
  - Family history vs. population/ethnicity based
- Predictive testing
  - Presymptomatic – likely future disease, e.g. Huntington's dx
  - Predisposition – increased genetic risk
- Incidental findings
  - Results returned while seeking other info

Uses of Genetic Data

- Individual results
  - Traditional – decision to test prompted by medical uncertainty and done after extensive discussion with trained genetics counselor
  - Direct-to-Consumer – autonomous decision independent of medical establishment
- Research
  - Following disease diagnosis
  - Recruited populations
  - Stored tissue samples

Do different uses of genetic data require different ethical lenses?

Traditional Medical Ethics

- Autonomy
- Beneficence
- Non-maleficence
- Justice

- Respect for persons
- Honesty

- Individualistic

- Doctor-patient relationship

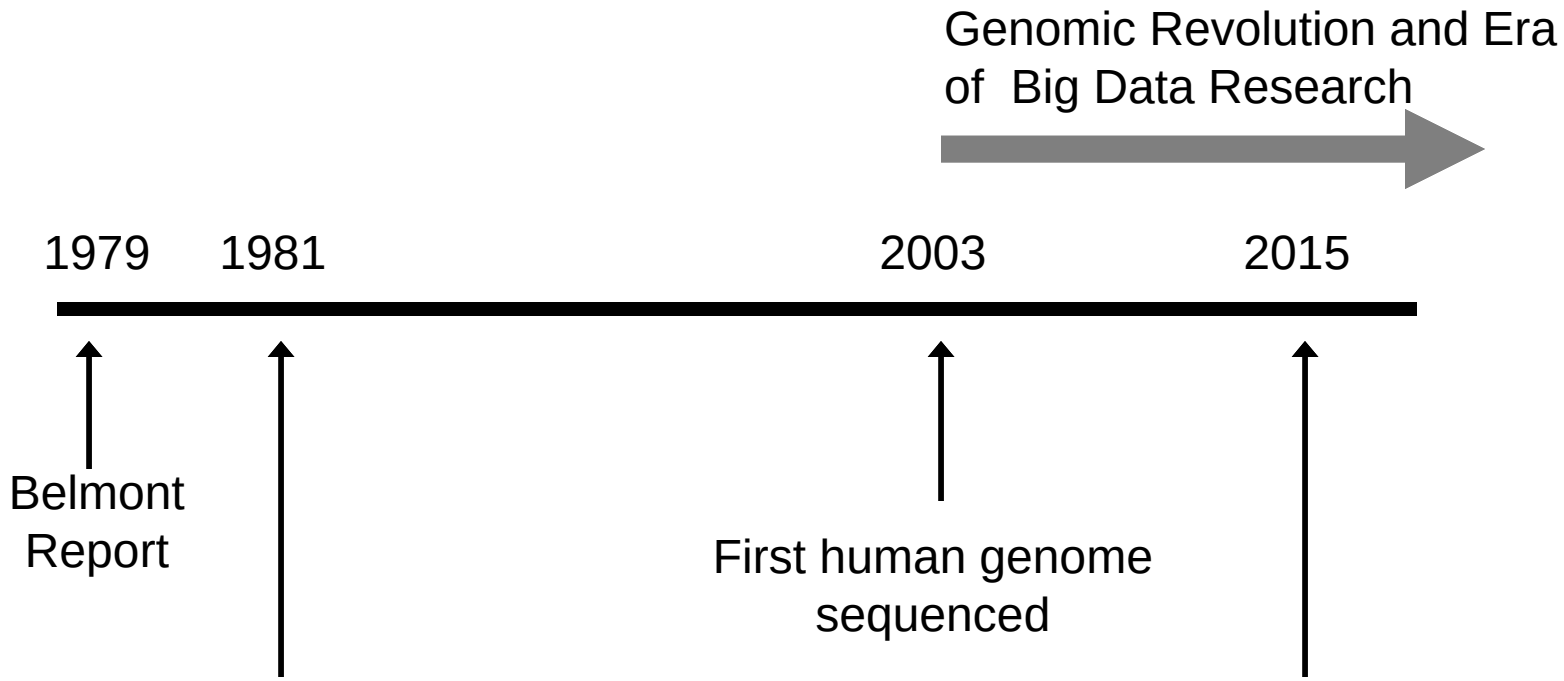
- Often described in term of conflict between principles

Public Health ethics

- Reciprocity
- Mutuality
- Citizenry
- Universality
- Utility
  - balancing benefits and harms/costs
- Building/maintaining trust

- Does not deny individualistic concerns
- Addresses populations, cultures and societies needs
- Provide framework for issues with many stakeholders

The Common Rule



Establishment of “The Common Rule”
Current human subjects research regulations adopted by the Department of Health and Human Services

Proposal to revise The Common Rule

Proposed Changes to the Common Rule

Current

- **No consent required for de-identified information or biological specimens**
  - No ability for withdrawal
  - No special considerations of pediatric populations

Proposed

- **Consent required for de-identified and identifiable biological specimens**
  - At time of collection
  - Open-ended consent for future unspecified research

COGR/APLU analysis of Comment Period

- NPRM ethical analysis
  - Increase Autonomy
  - Increase Trust
  - Increase Participation

- 67-79% of HD, registries, professional societies, etc opposed
  - "respecting autonomy at risk of patient lives"
  - Mandate of precision medicine

- 55% of general public opposed
  - Rebecca Skloot, *Your Cells, Their Research. Your permission?* NYT, December 30, 2015, author of the book *The Immortal Life of Henrietta Lacks*

A decision awaits,

MEANWHILE . . .

Changes to biopsy and excision consent

The UC Medical Center is dedicated to advancing medical knowledge to improve care for its patients. I understand that the procedures outlined below are necessary to support this mission and I consent to them. **However, I may cross out either or both procedures if I do not consent and it will not affect my care.**

I consent to the photographing or televising of the operation or procedure to be performed, including appropriate portions of my/the patient's body, for medical, scientific or educational purposes as long as my/the patient's identity is not disclosed. I understand that: 1) if I am conscious during a procedure, I can ask that the recording stop and 2) I can rescind (take back) my consent for use of this media up to a reasonable time before the images are used.

All specimens or tissues removed from my body that would otherwise be disposed of may be used for genetic and other research, or for scientific or educational purposes as approved by the Institutional Review Board of the University of Cincinnati Academic Health Center. No one except specifically authorized persons will have access to the tissue samples or information derived from my medical records. Every reasonable effort will be made to maintain confidentiality.

Additional comments:

So, what options are available to navigating ethical issues in the era of Big Data?

Biobanks

- repositories that assemble, store, and manage collections of human specimens and related data
- Existed in some form for ~70 years recent surge in number, size, and prominence has focused attention on the changing nature of biomedical research

ELSI* issues for Biobanks

- Models for informed consent
- Returning incidental findings
- De-identification, anonymization
- Secondary uses and research institutions
- Unanticipated concerns
- *Ethical, Legal and Social Implications*

Models for Informed Consent

Opt-In

- Traditional approach to human subject research
- High autonomy
- Refusal rates 4-40% for participation in biobanks

Opt-Out

- Used in multiple countries for consent to DD Tx
- higher utility and communality
- Increased participation may not reflect true desires of participants

Optimizing Opt-In

OPEN ACCESS Freely available online

PLoS one

Developing a Simplified Consent Form for Biobanking

Laura M. Beskow[1,2*], Joëlle Y. Friedman[3], N. Chantelle Hardy[3], Li Lin[3], Kevin P. Weinfurt[2,3]

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- Increase reciprocity and utility
  - plain language, 2 pages
  - Electronic version with “more information” and FAQ

Optimizing Opt-Out

Principles of Human Subjects Protections Applied in an Opt-Out, De-identified Biobank

Jill Pulley, M.B.A.[1], Ellen Clayton, M.D., J.D.[2], Gordon R. Bernard, M.D.[3], Dan M. Roden, M.D.[4], and Daniel R. Masys, M.D.[5]

- increase informed autonomous choice
  - Common central registration form
  - Educational materials
  - Approx 5% have opted out

Consent to future research

Approaches to Consent for future research with biospecimens

	TYPE OF CONSENT	DESCRIPTION
Less burden, less control	No consent	Do not obtain donor consent
	Blanket	Consent to future research with no limitations
	Broad*	Consent to future research with specified limitations
	Checklist	Donors choose which types of future studies allowed
More burden, more control	Study specific	Consent for each specific future study

*Framework proposed here couples initial broad consent with oversight and the possibility of ongoing communication

Grady C, et al. Am J Bioeth. 2015; 15(9)

Systematic review of Broad vs. Specific Consent

- Willingness
  - overall 85+% accept broad consent
- Preference
  - 52% preferred broad consent
  - 48% preferred study-by-study consent
- 78% of African Americans consented to genetic study in NHANES
  - 87% white/Cau.

Garrison NA, et al. Genetics in Medicine, 2016;18:7.

[a]s long as consent processes are equivalently effective in informing individuals about what they are consenting to, and as long as they do not unduly shape or undermine individuals' ability to make genuinely voluntary choices, there is no philosophical or ethical imperative to use one kind of consent process over another.

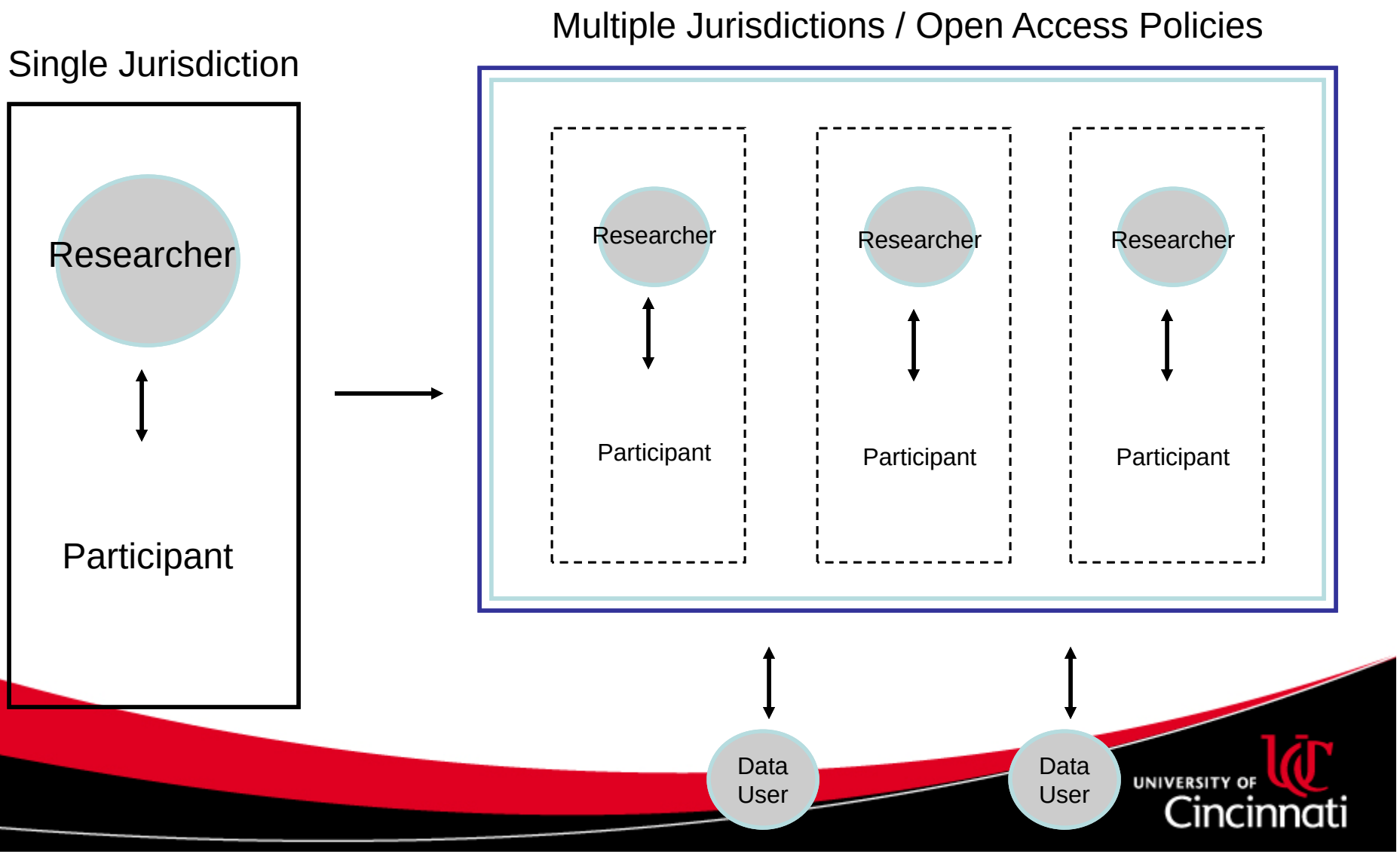
PCSBI, (2012, October), op cit, p. 92.

Privacy

- De-identification – separates patient identity from the researcher's knowledge
  - Able to be re-identified

- Anonymization – permanently separates primary identification from biosample/HER
  - Theoretically not able to be re-identified
  - proven ability to re-identify anonymized biodata

Secondary uses of Data



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Researcher – Participant relationship

Old Model

- Trust in relationships
- Privacy = secure location
- Goal – obtain high quality data for specific research question
- Disadvantage – high effort for limited result

New Model

- Trust in institutions
- Privacy = data security
- Goal – high quality information for many research projects
- Disadvantage - unexpected and undesired secondary uses
  - E.g. Havasupai tribe

Ethics and other biobank stakeholders

Survey of biobank managers:

- Concerns about secure funding
- Lack of planning if biobank closes
- Underutilization

President Obama State of Union Address 2015

- Research cohort of 1M+ Americans

PMI Working Group Recommendations

- Cohort assembly
  - voluntary
  - agree to re-contact, EHR access, biosample
  - Opt-in to secondary research
- Participant engagement
  - trust
  - ongoing feedback, representation on governance

PMI Working Group Recommendations

- Return of incidental findings
  - Return individual and aggregated results
  - Preferences on how much information
  - Option to change preferences
- Data Storage
  - Single centralized storage of all data
  - Common data model
  - Tiered data access for research

“If you build it, they will come”: unintended future uses

- Forensic investigations
- Civil Lawsuits
- Mass casualty events
- Border security/immigration
- Health resource rationing
    - GINA 2009
- Facilitating human rights abuses in autocratic regimes

Interesting, but what about my patients?

WGS- a once in a lifetime opportunity?

- Average exome has 3-8 medically actionable variants
  - Menu approach
    - Onerous to do pre-testing counseling for each dx
  - Panel approach
    - Choose groups (e.g. cancer, cardiac, neurological, carrier states)

Reporting Incidental Findings in Whole Genome and Exome Testing

- ACMG 2013 recommendations:
  - 56 genes for 24 conditions sought in every sample
    - Actionable, significant dx
  - Reported to physician without patient input
    - Irrespective of age or gender
  - "shared decision-making" regarding results
    - Updated to include Opt-out in 2014

Special concerns in genetic testing of children

- Best interests of child standard
- Assent vs. consent vs. co-consent
- “Right to an open future”
- Do parents have a “right to know”?
    - If most people are tested only once, should our responsibilities to children change?

Addressing pediatric ethical issues in genetic testing

- AAP policy statement 2013
  - Encourage genetic counseling
  - Parent permission/ child assent
  - Predictive testing for dx with childhood onset only
  - Routine carrier testing for childhood health benefits only
    - Reproductive genetic testing only for pregnant teen
  - Encourage parents in giving age appropriate information
  - Testing before adoption for child's best interest only

Recent ethical proposals for pediatric biobanks

- Acquire pediatric samples but don't use until re-consent at age of majority?
  - Destroy data of those unable to contact?
  - 18 year delay of data
- Extra-protection of identity?
  - publishing only location and approximate size of gene
- Return results to parents at time of test?
  - Only childhood vs. all variants?
  - Wait to release at age of majority?

Bedside Genetic testing in Dermatology

You are considering additional genetic profile test (Decision-DxMelanoma by Castle Bioscience) occur on the tissue obtained from wide local excision of a 1.27mm melanoma without histologically concerning features and negative SLNBx.

What ethical concerns in genetic testing should be addressed?

Patients and bedside genetic testing

- "I want to know what's in Pandora's box"
  - Professionals targeted **Justice** and **Beneficence**
  - Patient groups targeted **Autonomy,** **right to know**, accept consequences of anxiety
- Physician biases in offering genetic tests
- Address patient assumptions about genetics
  - May incorrectly assume that this test addresses risk of future melanomas
    - Risk of fatalism or false reassurance

Am J Med Genet 2012

Is financial burden an ethical concern?

From Melanoma.org support boards:

Re: Anyone have experience with the new DecisionDx test?

Hello,I actually just got my bill from Castle Biosciences after my gene expression test. The bill is for $7,918.00 and my insurance did not cover it. As you can imagine, I am freaking out a bit because my dermatologist said it wouldn't cost anything. I imagine my battle will start tomorrow finding out who gave me the wrong information. ☹ Robyn W - (1/26/2016 - 9:20pm)

Bedside Genetic testing in Dermatology

- After understanding the risks and benefits of the testing, the patient asks what the risk of recurrence is for the higher risk profile (class II). On hearing that the disease free survival was 38%, the patient asked to be tested but not be informed of his results.

How would you navigate his wish to not know his results?

Right to Not Know

- Autonomy in emotionally overwhelming situations?
  - Extend the decisional timeframe
- Is a “right to not know” incoherent?
- Are they being imprudent?
  - People receiving genetic testing for Lynch syndrome:
    - Choice seen as both autonomous and responsibility
    - Choice not to test judged negatively: selfish, imprudent, weak
  - Huntington’s Disease testing uptake 20%
    - Risks of adverse psychological events small

γνῶθι σεαυτόν

Know thyself

Thank you

- Marc Siegler, MD and the entire faculty of the MacLean Center for Clinical Medical Ethics at the University of Chicago

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- My first teacher of medical dermatology, Martha Housholder, MD and with Daniel Housholder, MD my first and best role models of the ethical practice of medicine

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