Clinical validity and utility of genome profies in risk assessment and control of CRC

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Goals of this meeting

Clinical goal:

Can "genome profiles…. assess individual risk for disease based on the combination of genetic variation at multiple loci."

Scientific goal:

What "scientific foundation for using personal genome files for risk assessment, health promotion and disease prevention."

Focus: "actionable information"

CRC Prevention Background

CRC in USA

- 150,000 cases/yr
- 50,000 deaths/yr

Risk over lifetime

- M: 5.7% incidence (2.3% death)
- F: 5.2% (2.1%)

Other

- 90% of CRC occur >50y.o.
- Only 1/3 detected at ‘curable’ stage
- adenomatous polyp common (30-50% >50y.o.)
- chemoprevention has limited role

CRC Prevention: What clinical questions and what kinds of ‘risk’; can genomics help

Clinical questions

1. What risk of CRC *over lifetime*?
2. What risk of CRC *now*?
3. What risk of CRC *in future,* over next X years?
   (e.g., after colonoscopy/polypectomy)

CRC Prevention: What clinical questions and what kinds of ‘risk’; can genomics help

Clinical questions

1. What risk of CRC *over lifetime*?
2. What risk of CRC *now*?
3. What risk of CRC *in future,* over next X years?
   (e.g., after colonoscopy/polypectomy)

For each question, consider:

- importance
- current approach (actions based on risk)
- potential of genomics

1. What risk of CRC *over lifetime*?

There are 3 risk groups:

- High
- Average
- Low

1. What risk of CRC *over lifetime*? **High Risk (e.g., APC/FAP)**

Definition

autosomal dominant (chrom. 5); small N

Importance

biology: elucidate biology of ‘common CRC’

clinical: ~get CRC in 20s

Approach

colectomy; action based on FH (though few have no FH), sigmoidoscopy

Potential of genomics in 2008

limited

1. What risk of CRC *over lifetime*?
Average Risk

Importance

- big N

Approach:

- screening (early detection)
  - colonoscopy, FOBT, sigmoidoscopy
  - screen >age 50
  - target: ‘early CRC’, ‘advanced adenoma’

Potential of genomics in 2008

- sort out, among ‘average’, who has higher/lower risk (‘tailoring’)

1. What risk of CRC *over lifetime*?

Average Risk

We already do some ‘tailoring’ in CRC screening.

What lessons?

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What lessons?

How do we manage ‘family history’?

Risk is, roughly, 2x ‘normal’.

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Average Risk

We already do some ‘tailoring’ in CRC screening.

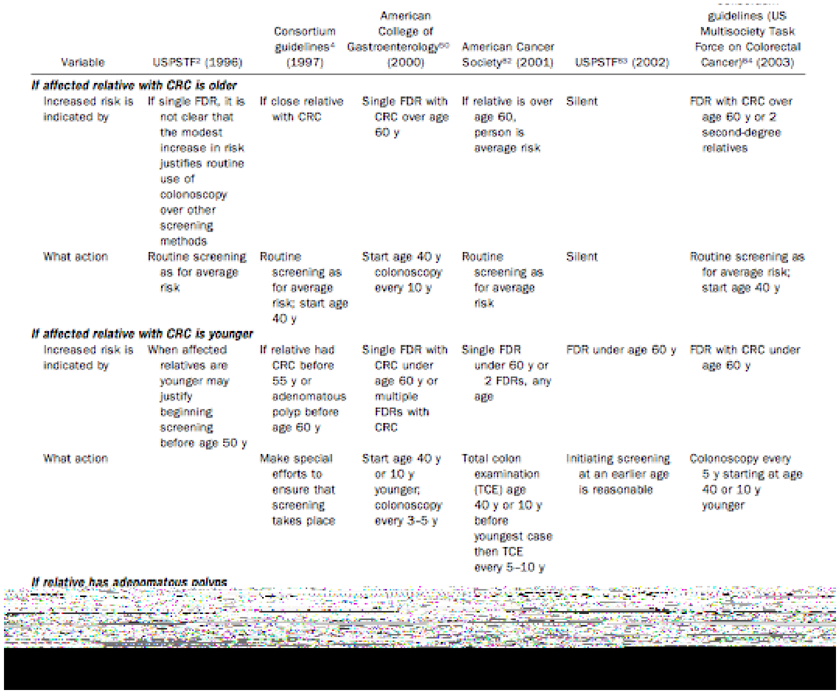
What lessons?

How do we manage ‘family history’?

Tailoring is based not on ‘genomics’, but genomics would give same kind of information about risk.

Family history: It’s a gigantic mess.

Table summarizes different groups’ recommendations



Variable	USPSTF[2] (1996)	Consortium guidelines[4] (1997)	American College of Gastroenterology[60] (2000)	American Cancer Society[62] (2001)	USPSTF[63] (2002)	guidelines (US Multisociety Task Force on Colorectal Cancer)[64] (2003)
If affected relative with CRC is older						
Increased risk is indicated by	If single FDR, it is not clear that the modest increase in risk justifies routine use of colonoscopy over other screening methods	If close relative with CRC	Single FDR with CRC over age 60 y	If relative is over age 60, person is average risk	Silent	FDR with CRC over age 60 y or 2 second-degree relatives
What action	Routine screening as for average risk	Routine screening as for average risk; start age 40 y	Start age 40 y colonoscopy every 10 y	Routine screening as for average risk	Silent	Routine screening as for average risk; start age 40 y
If affected relative with CRC is younger						
Increased risk is indicated by	When affected relatives are younger may justify beginning screening before age 50 y	If relative had CRC before 55 y or adenomatous polyp before age 60 y	Single FDR with CRC under age 60 y or multiple FDRs with CRC	Single FDR under 60 y or 2 FDRs, any age	FDR under age 60 y	FDR with CRC under age 60 y
What action		Make special efforts to ensure that screening takes place	Start age 40 y or 10 y younger; colonoscopy every 3–5 y	Total colon examination (TCE) age 40 y or 10 y before youngest case then TCE every 5–10 y	Initiating screening at an earlier age is reasonable	Colonoscopy every 5 y starting at age 40 or 10 y younger
If relative has adenomatous polyps						

From Ransohoff D. Gastroenterology 2005;128:1685-95

Can stool DNA test detect CRC?

Answer:

1. Yes, but not well: sensitivity 51%; specificity 95%
    - a lot better than fecal occult blood testing
    - but test is expensive
2. SO can biological approach be improved?

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Mother Nature fools us again!

Goals of this meeting: what *research agenda for CRC*

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what *research agenda for CRC*

1. Is field of CRC prevention ‘ready’ for genomic information about risk?
   - no quantitative conceptual framework
   - ‘family history’ situation illustrates not only lack of data, but also lack of framework to handle it
2. HOWEVER, one potential use of genomic information about lifetime risk that is clinically important:
   - *Can a* low-risk *group be identified that does* not *need screening?*

This potential use is neat, clean, clinically important

This potential use is: neat, clean, clinically important

.. and meets Khoury criteria (Genomics 2008)

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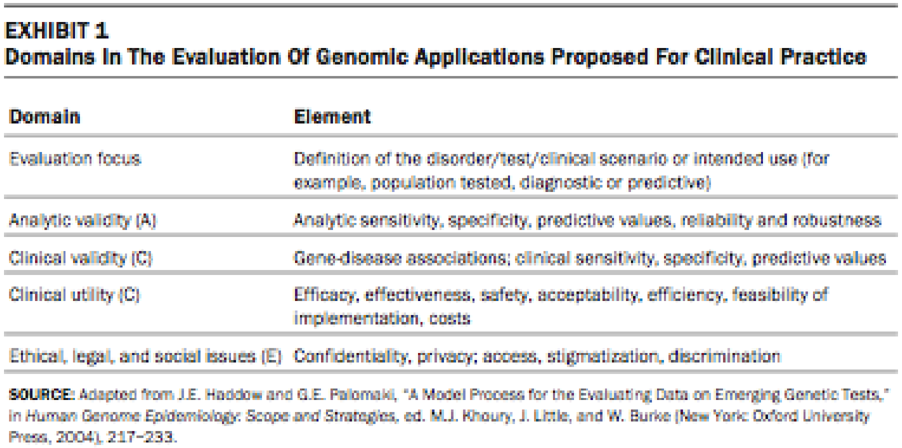

EXHIBIT 1
Domains In The Evaluation Of Genomic Applications Proposed For Clinical Practice

Domain	Element
Evaluation focus	Definition of the disorder/test/clinical scenario or intended use (for example, population tested, diagnostic or predictive)
Analytic validity (A)	Analytic sensitivity, specificity, predictive values, reliability and robustness
Clinical validity (C)	Gene-disease associations; clinical sensitivity, specificity, predictive values
Clinical utility (C)	Efficacy, effectiveness, safety, acceptability, efficiency, feasibility of implementation, costs
Ethical, legal, and social issues (E)	Confidentiality, privacy; access, stigmatization, discrimination

SOURCE: Adapted from J.E. Haddow and G.E. Palomaki, "A Model Process for the Evaluating Data on Emerging Genetic Tests," in *Human Genome Epidemiology: Scope and Strategies*, ed. M.J. Khoury, J. Little, and W. Burke (New York: Oxford University Press, 2004), 217–233.

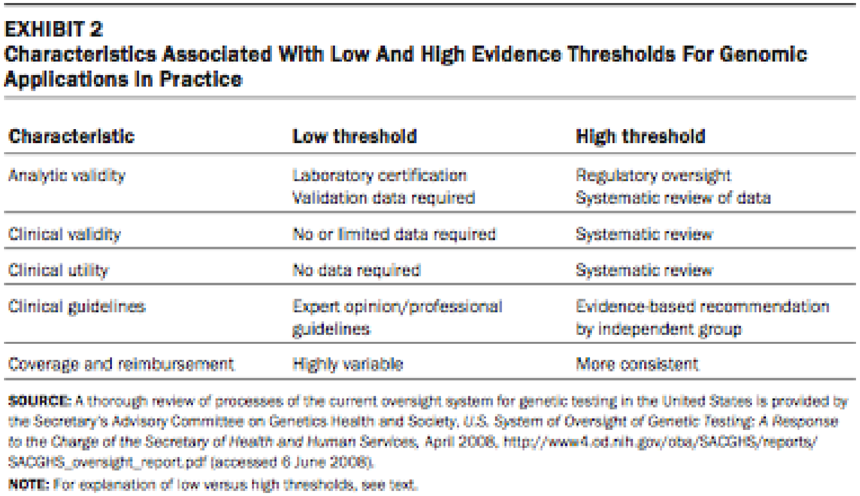

EXHIBIT 2
Characteristics Associated With Low And High Evidence Thresholds For Genomic Applications In Practice

Characteristic	Low threshold	High threshold
Analytic validity	Laboratory certification Validation data required	Regulatory oversight Systematic review of data
Clinical validity	No or limited data required	Systematic review
Clinical utility	No data required	Systematic review
Clinical guidelines	Expert opinion/professional guidelines	Evidence-based recommendation by independent group
Coverage and reimbursement	Highly variable	More consistent

SOURCE: A thorough review of processes of the current oversight system for genetic testing in the United States is provided by the Secretary's Advisory Committee on Genetics Health and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, April 2008, http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf (accessed 6 June 2008).

NOTE: For explanation of low versus high thresholds, see text.

end