Genetics and Research Ethics: where are we now?

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Research Ethics Education Day:
'20/20 Adjust Your Lens'
January 27, 2020

www.bhphotovideo.com

Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.

Education about inheritance, testing, management, prevention, resources and research.

Counselling to promote informed choices and adaptation to the risk or condition.

Resta, R., Biesecker, B.B., Bennett, R.L. et al. J Genet Counsel (2006) 15: 77

BC CANCER HEREDITARY CANCER
Provincial Health Services Authority

Reduce the morbidity and mortality from hereditary cancer syndromes

Find people with hereditary cancer syndromes

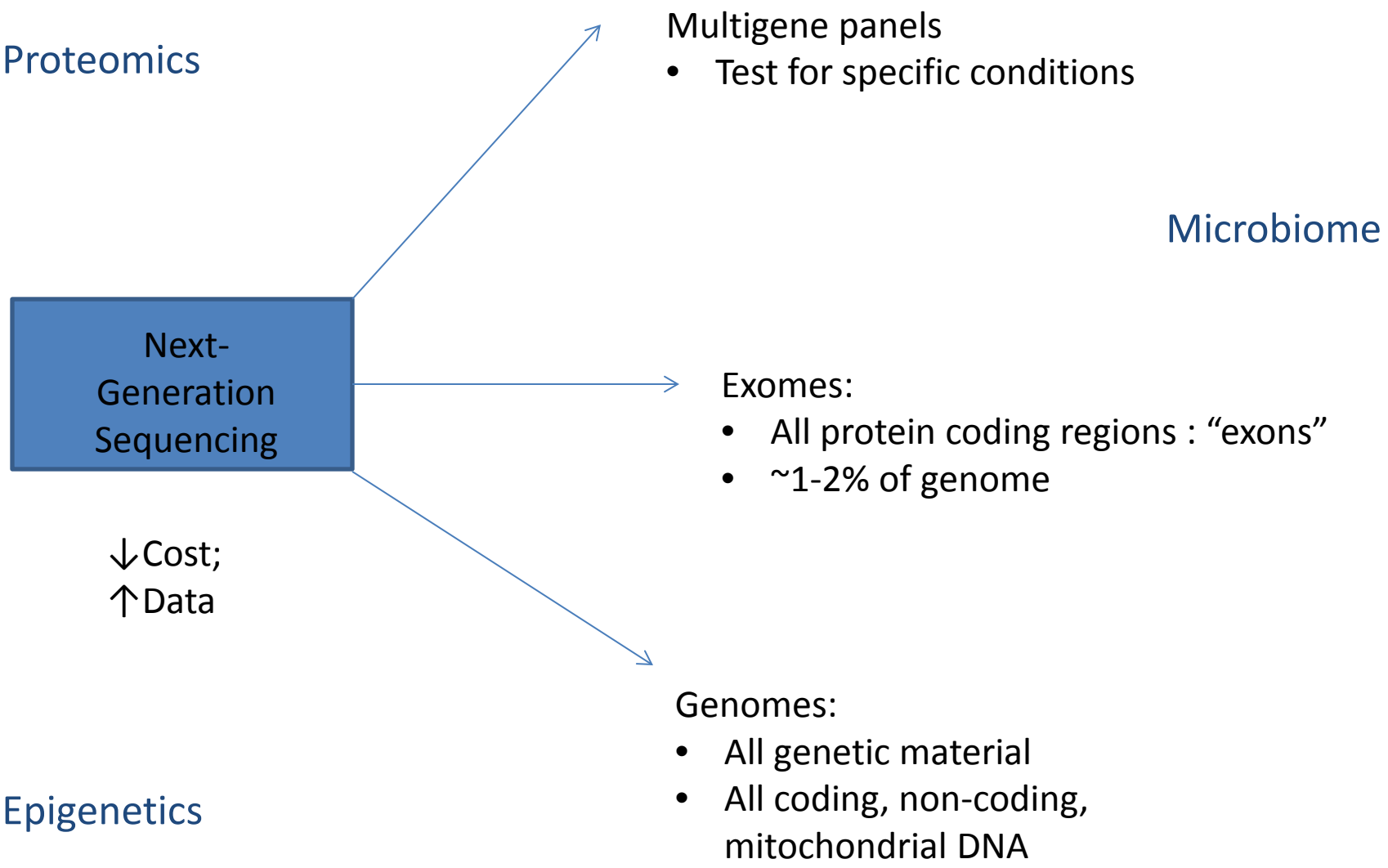
Provide risk management advice

Help with cancer treatment decisions

Identify resources and supports

- Skillsets: scientific, medical, psychosocial, ethical, family
- Team: medical geneticists, molecular geneticists/labs
- Serve as educators and resource people for other healthcare professionals and for the general public.
- Evolving role: research, laboratory, policy, education, administration, advisory, advocacy, marketing/consulting

All have benefits, limitations and most appropriate uses!



How does genomic sequencing work?

- Sequence: ~ 3,000,000,000 DNA pairs that are our body's instructions for functioning

- Sometimes, just ONE change ("variant") in one DNA letter can cause devastating problems

- There are also deletions, insertions, rearrangements, repetitive elements….

Patricia Birch, UBC

The human genome is very variable

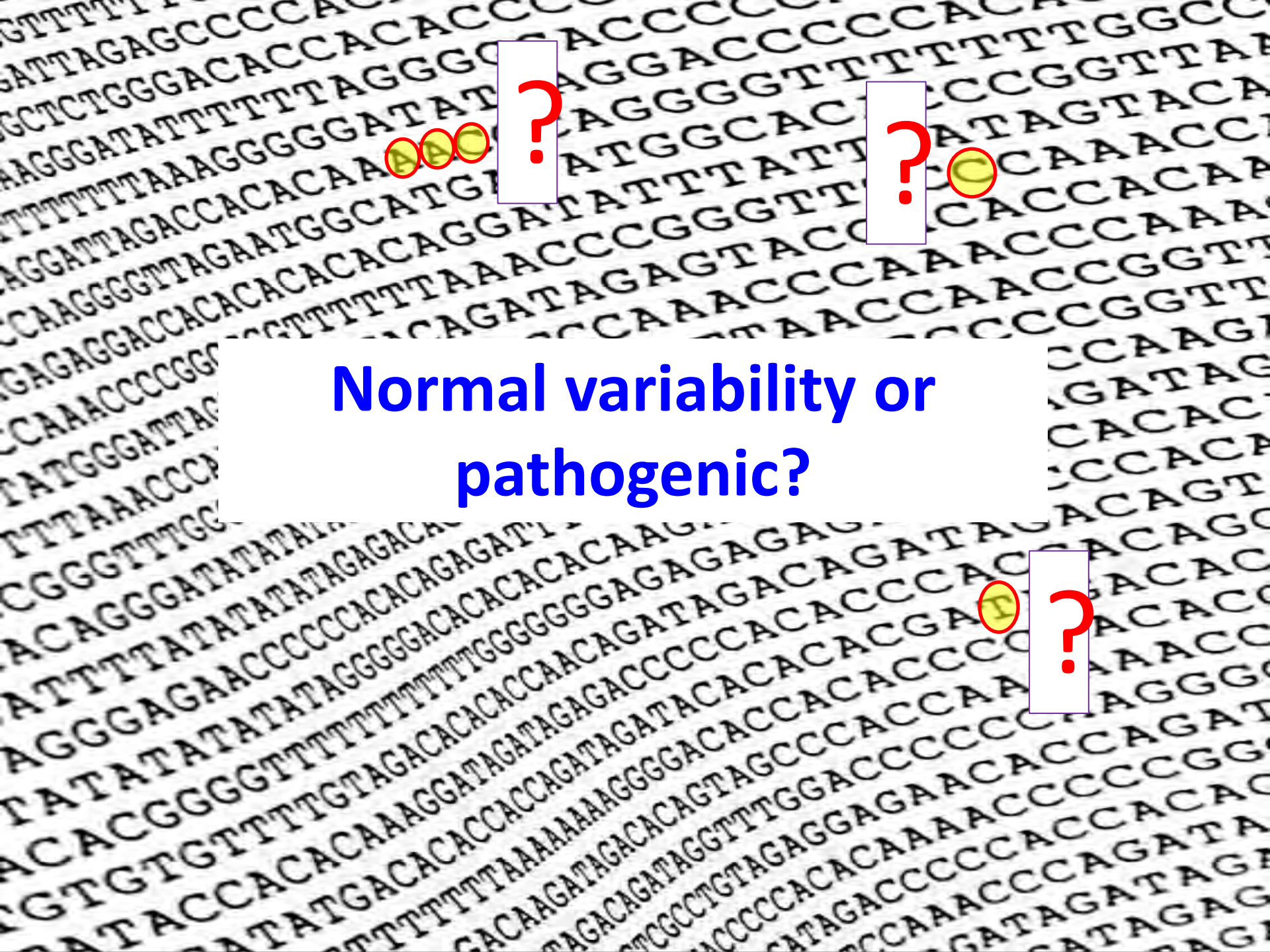
We are “only” 99.9% the same as each other.
The remaining 0.1% is mostly normal variability.

Here is one variant:

Me: `aatgcctatagggggcadaaaaccc`

You: `aatgcctatagggggcadaaatccc`

Patricia Birch, UBC

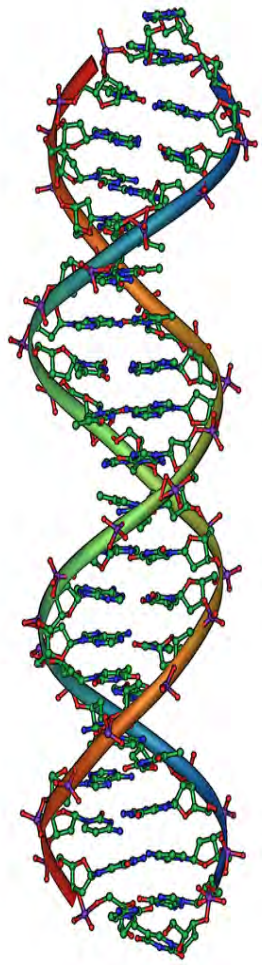

?
?
?
Normal variability or pathogenic?

There is no “perfect genome”!

There is no single “perfect human” string of DNA that we can use as a reference.

We need to look at databases that contain DNA sequences from many, many healthy people.

Compare each of the patient’s millions of variants to those seen in the reference database.



Patricia Birch, UBC

Where does the variability come from?

A new variant can originate in the person being tested (egg or sperm or early embryo)

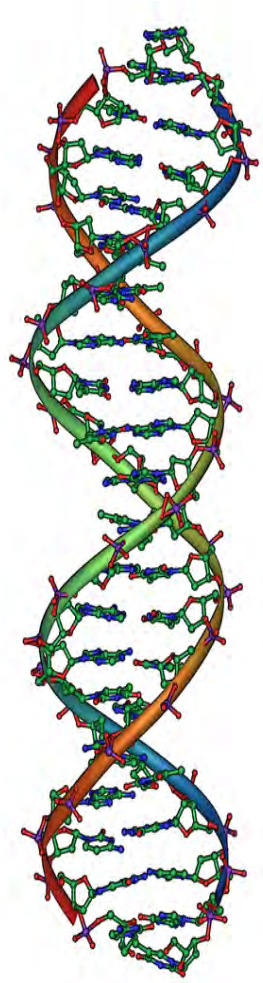
OR

Inherited from parents…

and from their parents…

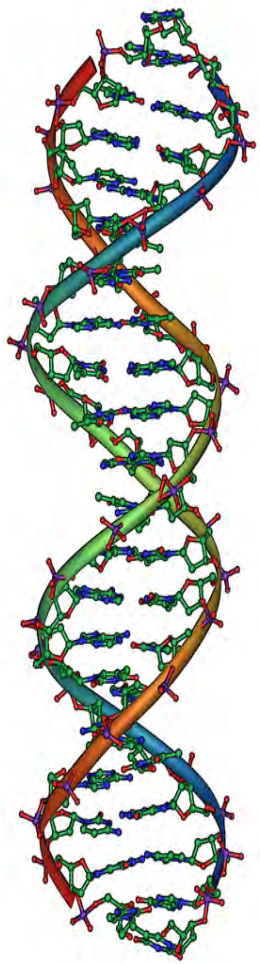
and from their parents…

We are most similar to those we are most closely related to – parents …….. distant cousins….. shared ancestors



Patricia Birch, UBC

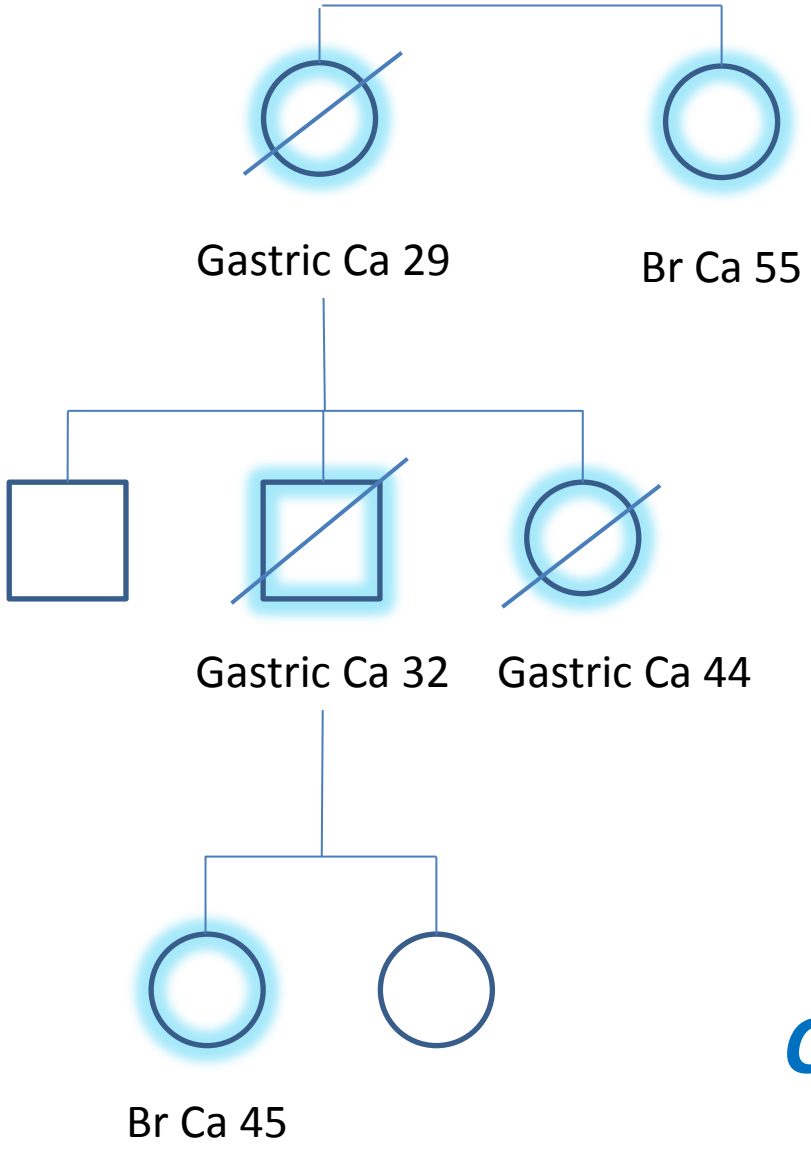
Need reference databases that contain many sequences from people of the same ancestral group as the person being tested.



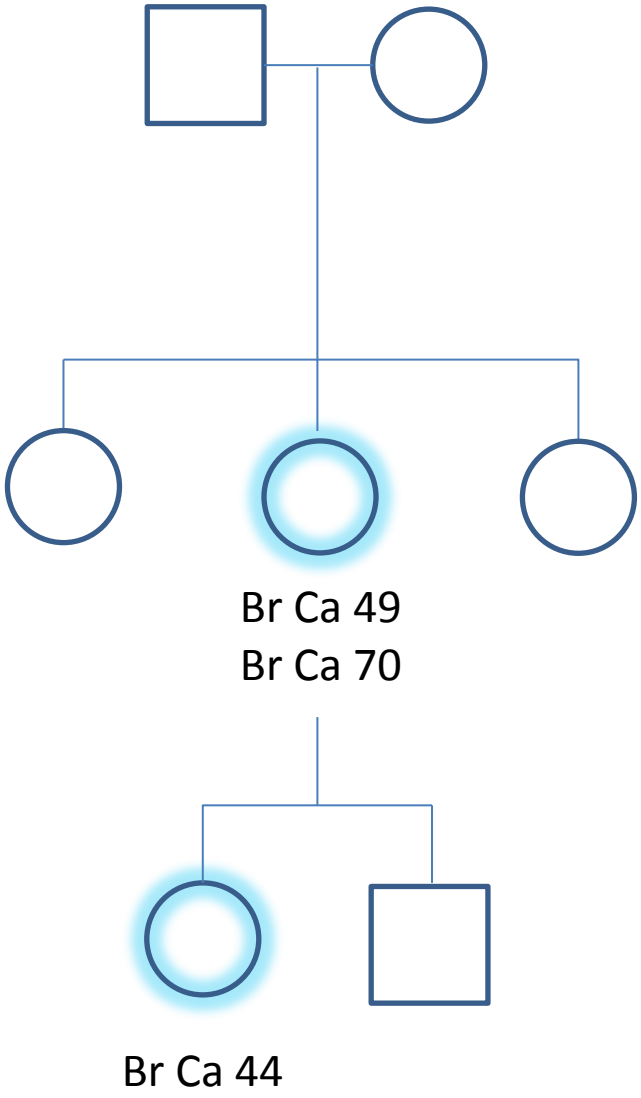
Patricia Birch, UBC

Who in society does current genetic research benefit the most?

- Variant identification vs **variant interpretation**
  - Not all tests created equal – **data quality!**
  - P/LP ("mutation"), **VUS**, LB/B:
    - Classification
    - Not static!
    - Penetrance may be context-dependent
  - 'Negative' result doesn't mean nothing is there or that disease won't occur
  - Are results generated (or confirmed) in clinically accredited laboratories?
- Secondary findings: information that extends beyond aims and objectives of the test


Gastric Ca 29
Br Ca 55
Gastric Ca 32
Gastric Ca 44
Br Ca 45

CDH1


Br Ca 49
Br Ca 70
Br Ca 44

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

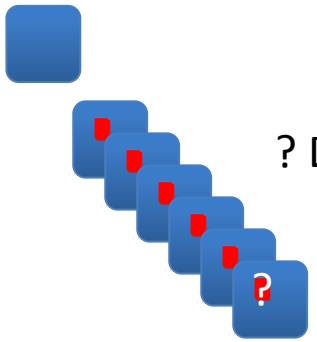
False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care

Stephany Tandy-Connor, MS, Jenna Guiltinan, MS, Kate Krempely, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigette Tippin Davis, PhD, FACMG

Genetics in Medicine **20**, 1515–1521 (2018)

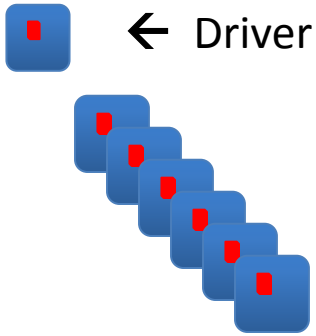
Somatic vs germline

Sporadic cancer



? Driver mutations, initial molecular lesions

Hereditary cancer



← Driver mutation; **this is the initial molecular lesion**

Dr. Barbara Biesecker, Genetic Counsellor
RTI International (non-profit research institute)

ASHG 2019
ANNUAL MEETING
HOUSTON • OCTOBER 15-19

Educating Health Care Providers in Genomics to Meet Patient Needs

Barbara B Biesecker, PhD
RTI International

Zoe Lohn, HCP

ASHG 2019
ANNUAL MEETING
HOUSTON • OCTOBER 15-19

What Do Clients Not Understand?

- Limited data reveals clients' misunderstandings
- Genetic constructs—cells, chromosomes and genes
- Probabilities—patients can restate the risk the GC relayed but their risk perception often differs
- Uncertainties as a state of science discovery (rather than professional ignorance)
- Consequences of a finding—may imbue a VUS as meaning no risk or given that it is "something," an increased risk

Zoe Lohn, HCP

ASHG 2019
ANNUAL MEETING
HOUSTON · OCTOBER 15-19

"GCs should focus on the consequences of genetics rather than scientific concepts"

Critique of Genetic Counseling

- Evidence demonstrates that genetic counselors are eager in teaching patients and often use highly technical language (Roter et al., 2009; 2007 Ellington et al., 2011, Joseph et al., 2015, 2016)
- Counselors may provide too much information—describing chromosomes, cells and genes that mean little to patients/clients
- Information is inconsistently tailored to what the client already knows
- The health literacy level of the information is high
- And probabilities may be presented in less effective ways
- Genetic counseling has laudable aims, and can benefit from evidence from health communication, adult education and communication science to enhance exchange.

Are research consent forms and conversations framed in plain language?
How is patient understanding assessed?

Zoe Lohn, HCP

Informed Consent

- Patient comprehension, decision-making capacity, voluntariness and adequate information.
- Challenges arise with genomic sequencing given its complexity, inability to explain/predict all possible results and clear risks/benefits may be unknown.
- Historical standards of consent may be difficult to apply.
- Alternative models needed.

Return of Results

In first 2 years of Stanford Research Ethics Consultation services, 50% of triggers related to return of findings dilemmas.

- Rules may apply at different levels in different jurisdictions (eg. Human subjects research, biobanks, clinical trials, genomic sequencing, genetic/individual data).
- Different thresholds for utility (medical, familial, reproductive and/or personal).
- Requirements for data quality, variant assessment, effective communication of results are evolving in uneven ways. Growing gap between researchers with the expertise, infrastructure and resource to meet these requirements.

“Should” or “May” in Policy/Law

- Conditional:
  - Analytical/clinical validity
  - Clinical actionability
  - Individual consent to receive results/volition
  - Availability of care or counselling resources

- Drawing on duty to rescue/warn, reciprocity, individual autonomy, beneficence.

- Participant/individual
  - Personal utility
    - Affective, cognitive, behavioural
    - Life and family planning, relief and justification, self-knowledge, self-determination
- Family
  - Concept of personal vs family information
  - Who is the ‘research subject’?
  - Participant privacy and confidentiality vs duty to warn (?less in research)
  - Eloquent arguments for and against
  - Results return plan made with IRB and medical professionals qualified to discuss findings, inform participants, minimize harm.
  - Postmortem considerations

- “Right to know”
  - Underpins policies requiring researchers to return clinically relevant information.
  - Or ‘right to access’ – implies request must be made

- “Right not to know”
  - Implemented by offering choice, eg. an opt-out.
  - Role to override wishes to avoid ‘serious harm’ to participant or their relatives

What qualifies as relevant/serious health information, who decides and what qualifies as an unequivocal desire not to know?

Who should review results before they are returned? Who returns them? Is timely access to genetic counselling available for 'significant' results?

'Therapeutic misconception': harm from assuming no results from research means 'everything is okay' or, believing there will be personal benefit from return of results.

In genomics, what is significance of variant? May be misinterpreted by participant or their health care providers. Most common reason for recommending against return of results (scientific validity or utility) – uncertainty will increase with resource, infrastructure or expertise limitations.

- Consent
  - Provide participants with information about return of results during consent process
  - What will be returned and how
  - Can offer choices/tiered approach
  - Opportunity to update preferences?

- Establish a plan for the return of individual results for prior REC approval,
- Inform participants of this approach,
- Clarify the choices available to participants,
- Use a qualified genetic testing laboratory for validation,
- Explain any limitations on possible return (nature of WGS results to be returned, by whom, when, and over what period of time),
- Mention possible familial, reproductive/carrier and insurance implications, and
- Provide a process for expert determination of "action-ability" if return is foreseen.

GNA, 2017

In our view, respecting individual choice—informed by the broader familial and social implications of WGS—is primordial but must be tempered and balanced by the needs of efficient, economic, and ethical research and health care. This common goal illustrates the "right of everyone to share in scientific advancement and its benefits" (art. 27 Universal Declaration of Human Rights, 1948). A return of results policy should serve to support the realisation of this right. To keep step, harmonised, systematic approaches must be developed to accelerate the transmission of lessons learnt, clarify approaches, improve individual outcomes, and ensure the efficacy and sustainability of health care systems.

Secondary Findings

- Broad agreement that at least some of these should be returned to participants.
- Often “actionable” P/LP: supported by participants, clinicians and society.
  - Challenges raised in context of adult-onset conditions identified in children.
- Limitation of current literature: varied definitions of SF and actionability; hypothetical scenarios
- Sapp et al AJHG (2018): n = 1200, 14 SF in 18.
  - Returned by GC, referrals made to local specialists
  - Minimal psychological distress; 9 accessed recommended health services.

Research needed!

"Health outcomes, utility and costs of returning incidental results from genomic sequencing in a Canadian cancer population: protocol for a mixed-methods RCT". Shichk et al. BMJ Open 2019; 9.

- All will receive cancer related results; intervention arm will have option for incidental findings.
- Primary outcome: psychological distress at two weeks post results.
- Secondary: behavioural consequences, clinical and personal utility over 1 year, health service use and costs at 12 months and 5 years.
- Qualitative interviews with participants and providers.
- Will also recruit relatives and care providers for family "spill-over" effects and care consequences and costs: cascade effects on health services and family systems.
- Develop educational materials.

- Re-interpretation of results
  - Evidence base supporting genetic sequence variation interpretations constantly evolving
  - Variant's clinical significance can be reinterpreted
    - Revision of an interpretation:
      - eg. LP to P, VUS to LP, VUS to LB
    - Re-analysis, new data published
    - Majority downgrades – as allele frequencies in diverse populations documented, more rigorous classification criteria implemented.
    - Some can impact clinical management (screening, treatment, family implications)
  - Responsibility to re-contact?
    - Ethical, legal and financial issues
    - Majority of stakeholders consider this ethically desirable, practically difficult
    - No "duty to hunt"

ASHG Position Statement 2019

- Maximizing benefits and minimizing risks to research participants needs to be weighed against the overall aim of research: to generate new and important scientific knowledge.
- Ethical obligation is stronger when:

  - The research is active, ongoing, and has funding and the participant's contact information is up to date (practicability);
  - Informed consent set the expectation for potential re-contact (respect for persons and autonomy);
  - There is a high degree of certainty about the new interpretation and/or implications of a changed interpretation, as judged by both investigator and IRB or governance structure (non-maleficence); and
  - The reinterpretation would be relevant to the condition under study or, in the case of an actionable incidental finding, likely to change medical management (beneficence).

Box 1. Recommendations for Recontacting Participants after Reinterpretation of Genetic and Genomic Research Results

1. The ASHG *strongly recommends* attempting to recontact participants to offer updated results if the reinterpretation is related to the phenotype under study or is reasonably expected to affect a research participant's *medical management.*
2. If the reinterpretation is *not expected* to affect management, recontact is advised, rather than strongly recommended, for correction of the classification of a variant previously reported to the participant and whose pathogenicity classification has changed from or to pathogenic or likely pathogenic.
3. The ASHG recommends that there is no responsibility for researchers to hunt or scan genetic and genomic data or literature for changes in variant interpretation.
4. The ASHG recommends that any *responsibility* to recontact research participants is limited to the duration of research funding. Recontact after the conclusion of funding may be *desirable* if sufficient resources exist.
5. The ASHG recommends that no responsibility to recontact participants exists when the IRB protocol associated with the study closes or identifiers are stripped, rendering further recontact infeasible.
6. The ASHG recommends that, when there is a strong recommendation for recontact, the recontact should occur within 6 months of the reinterpretation.
7. The ASHG recommends that instances of recontact be documented.
8. The ASHG recommends that any responsibility for recontact is limited to a "good faith effort" to reach the participant within the limits of existing constraints, including (but not limited to) financial and personnel resources, the existence of accurate contact information for the participant, and willingness of the participant to accept recontact.
9. The ASHG recommends that research projects develop a plan not only for initial return of results but also for return (or not) of reinterpretations of those results. As part of that plan, research participants should be alerted to the likelihood that interpretations of results might change over time and be given the opportunity to provide informed consent regarding the plan for return of results, including initial and reinterpreted results.
10. The ASHG recommends that, if the participant consented to any return of results at the time of original research consent, then consent to recontact for the same type of results is implied and therefore appropriate subject to the other recommendations in this policy statement.
11. The ASHG recommends that, ideally, the same individuals and communication methods that were used for the initial return of results should be used for recontact.
12. The ASHG acknowledges that in the research context, participants might consent to initial return of a much wider range of results. Thus, it is appropriate to return reinterpretations derived from reanalysis broader than those addressed in this statement when that is consistent with study design and consent documents.

1. The ASHG *strongly recommends* attempting to recontact participants to offer updated results if the reinterpretation is related to the phenotype under study or is reasonably expected to affect a research participant's *medical management.*

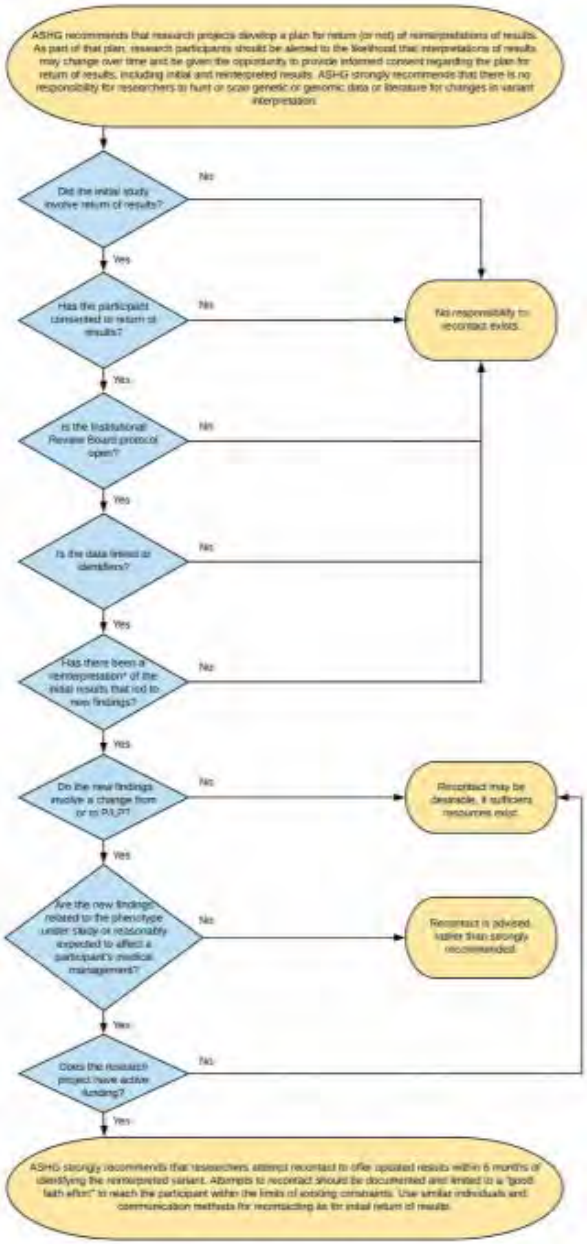
- serious conditions
- highly penetrant variant
- effective intervention available (screening or treatment)
- risk/benefit profile of intervention is favorable
- strong knowledge base about condition overall

*applies to primary and additional (eg. secondary/incidental) findings
*researchers responsible for the validity of variant classification/critical evaluation of source of new evidence
*to be considered from perspective of researcher but should be informed by clinical guidelines and, when practical, consultation with a clinician.

10. The ASHG recommends that, if the participant consented to any return of results at the time of original research consent, then consent to recontact for the same type of results is implied and therefore appropriate subject to the other recommendations in this policy statement.

Develop a plan for re-contacting research participants in the future and include it in the consent form; include an option to decline future contact entirely.

If consent documents for existing study do not address issue of re-contact or return of results turn to Research Ethics board/consultation service for guidance.



*Reinterpretation refers to both reclassification of variants and reanalysis of original data (per section *What does it mean to reinterpret results?*)

Figure 1. Recommended Pathway for Considering Recontacting Participants after Reinterpretation of Genetic and Genomic Research Results

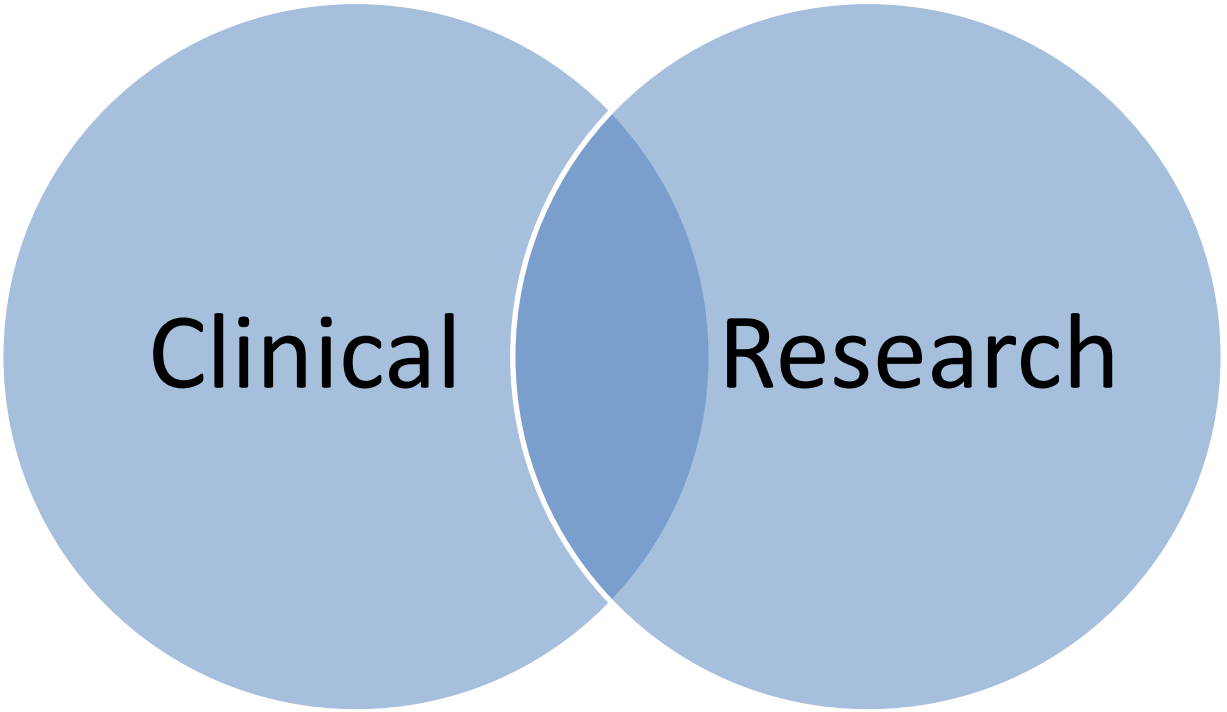
- How?
  - Personal appointment, telephone call, letter, portals
- Research needed!
  - Benefits, risks, costs, procedures, outcomes of recontact

Participant/Societal Perspectives – Key!

- Want genomic findings disclosed.
- Increases when the information pertains to life-threatening disease, **high penetrance**, lifestyle changes as prevention, high **effectiveness of prevention**.
- Many hold that genomic results relevant to a family member's health should be offered. Most have few concerns about sharing genetic information; rather, their concerns focus on health consequences of not sharing.
- A focus on respect for individual privacy – without attention to how the broad social and cultural context shapes preferences within families – cannot be the sole foundation of policy.

'Genomic medicine' = 'medicine'; one more option in the toolkit.

“Clinical” vs “Research”



Joint decision-making model with research ethics committees involving experts in the field independent of the research study including clinical and molecular genetics professionals.

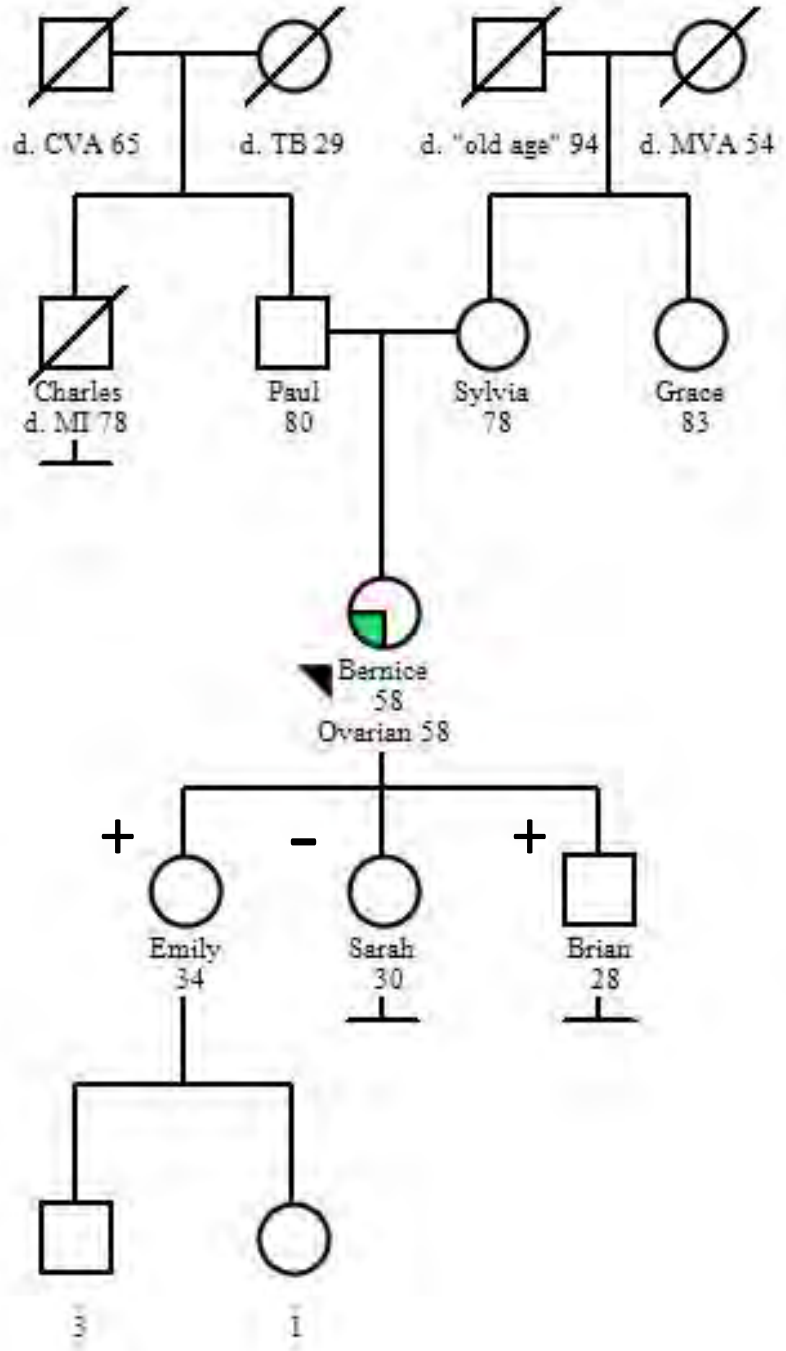
“We are starting a study on urinary and stool microbiome in patients undergoing immunotherapy for bladder cancer here at XXX. The name of the study is XXX and study # is XXX. **As we are doing genetic studies on study participants’ samples, there is a possibility that we find clinically significant incidental germline mutations,** that may require us to do a referral on such occasion to BC Cancer Hereditary Program.

We are currently undergoing Research Ethics Board approval process and they have asked us to inform you about this possibility.

Is there any more information you need regarding our study? We will commence our study as soon as we get approval, most likely Feb 2020”.

BRCA2 VUS

BRCA2



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Provincial Health Services Authority