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Engaging with the public on whole genome sequencing in NL

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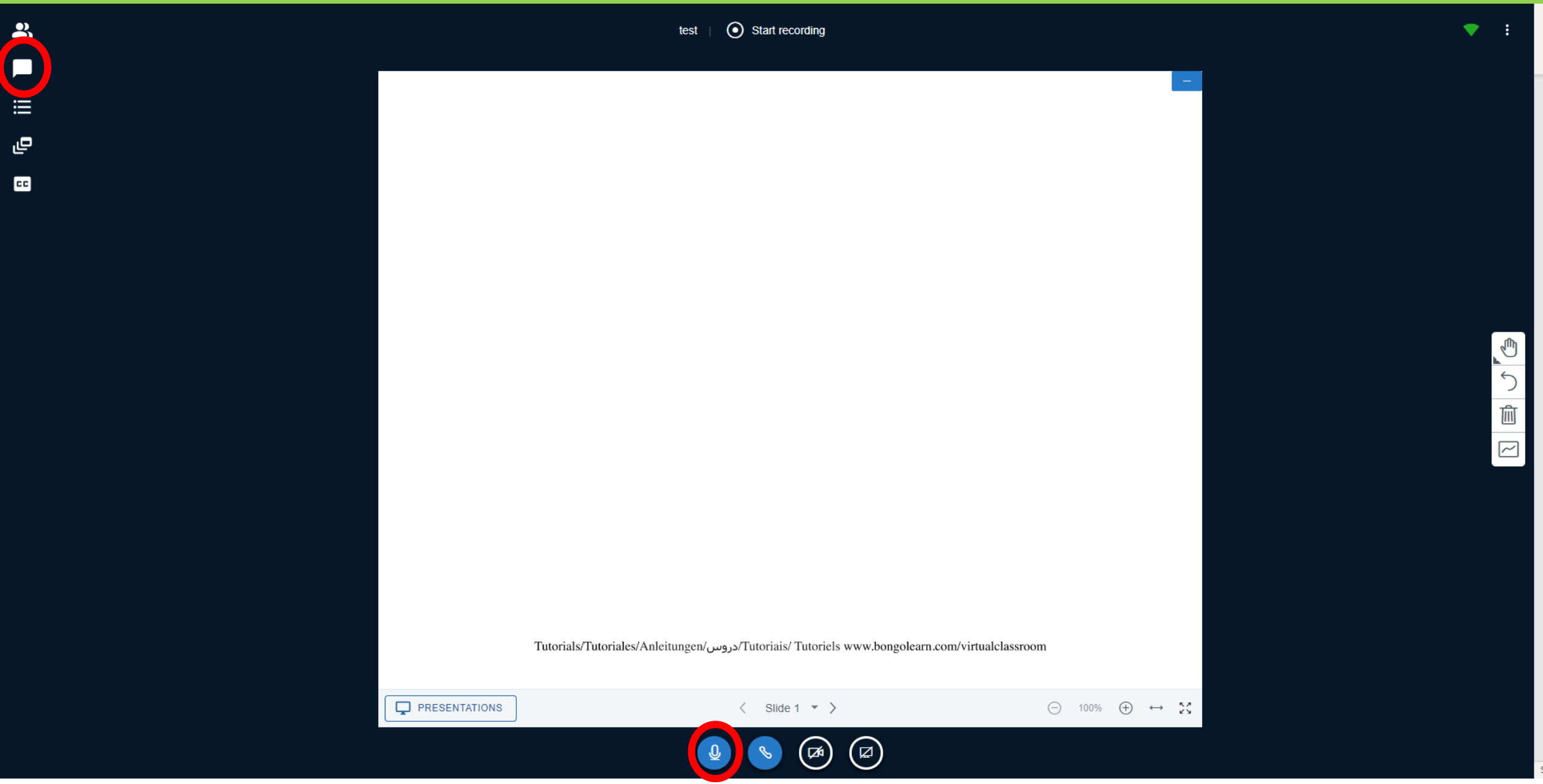

Engaging with Newfoundlanders and Labradorians about genome sequencing

HOLLY ETCHEGARY, PHD, FACULTY OF MEDICINE

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First, back to basics - What is a genome?

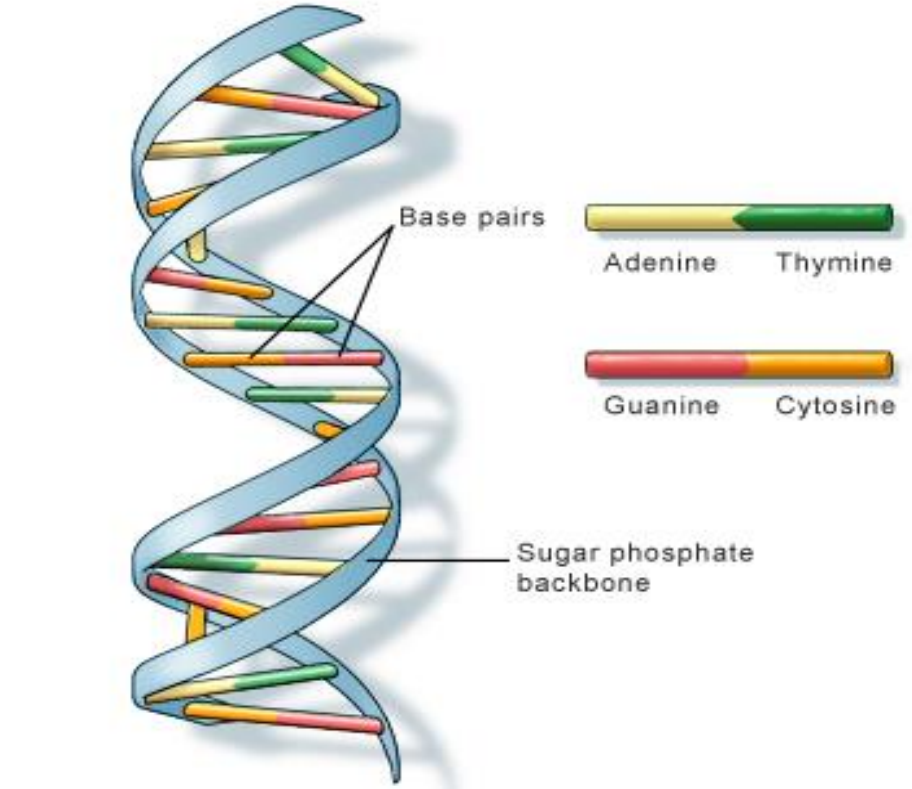
- The instructions for making and maintaining you
- Written in a chemical code called DNA.
- Your genome is all **3.2 billion letters** of your DNA. It contains around **20,000 genes**.
- Genes are the instructions for making the proteins our bodies are built of – from the keratin in hair and fingernails to the antibody proteins that fight infection.

What is DNA?

DNA (deoxyribose nucleic acid) is a long molecule. It has a twisted, double helix shape.

DNA is made up of four different chemicals, or bases. These are represented by the letters A, T, C and G. The bases are attached to two phosphate backbones.

The bases are paired together; A with T, G with C. The two backbones twist around each other to give the characteristic double helix.



What is genome sequencing?

- Sequencing is a technique that is used to 'read' DNA. It finds the order of the letters of DNA (A, T, C and G), one by one

- Sequencing a human genome means finding the sequence of someone's unique 3 billion letters of DNA

What is exome sequencing?

- Here, only the sequence of letters from all the protein-encoding genes are read
- Thus, only the subset of DNA that encodes proteins is selected – about 1% of the genome or 30 million base pairs
- It is a little quicker and slightly less expensive than sequencing the entire genome

Increasing use of next generation sequencing – whole genome or exome

- Decreasing cost and time has seen the use of next-generation sequencing technologies in a variety of contexts – research, clinical and commercial (e.g., 23&me or ancestry.com)
- Currently, used clinically in the diagnoses of rare genetic disorders and in personalized drug therapy, most often in oncology
- The literature suggests, however, the use in clinical practice and research will continue to grow

Pharmacogenomics

- Pharmacogenomic technologies try to detect genetic variations in a patient, or among patient populations, to help doctors select the drug compounds and doses that are most likely to work

- For example, a pharmacogenomic drug, Herceptin, is a highly effective therapy in the 15 to 25 percent of breast cancers that have a particular genetic variant that causes marked overexpression of the HER2 protein (a cell growth promoter) and is virtually useless against breast tumors without that variant

Challenges with routine use in practice

As noted, sequencing most often used clinically in oncology and rare diseases

- Technical limitations prevent identifying all disease-associated variants
- Data on what a particular variant actually means clinically may not be available – thus, clinical utility is still low
- Controversy remains about what variants should be reported to patients and their providers – what about for secondary findings?
- Complexity - concerns that patients and providers may not understand results or act inappropriately on them
- Long-term psychosocial outcomes of sequencing are largely unknown

Despite concerns….

- Genome data are already being collected in a large scale and mined for scientific discovery – big samples are needed (e.g., Genome England, the US's All of Us program of research)

- Increasingly, genomic research is being conducted through large, multi-site consortia and being linked to electronic medical records and other tissue or blood samples

eMERGE – Electronic Medical Records and Genomics Network

- US based, funded by the National Human Genome Research Institute
- Established in 2007; multiple sites/hospitals
- Has now published a collection of literature, including lessons learned

- Their experiences raise ethical, legal, social and policy issues that could arise with the use of WGS in our province – Consent models? Return of secondary findings? Pre-sequencing counseling available? Capacity to store results?

Sequencing in NL?

- Traditionally, samples sent outside the province for sequencing, largely ordered by provincial medical genetics
- But - NL now has a next generation sequencer – theoretically, we can now sequence genomes on site
- Ongoing discussion amongst relevant stakeholders (provincial gov't, health authorities, MUN, privacy offices, researchers, providers, etc.) continues
- Governance frameworks, privacy frameworks, informed consent policies, return of results, and so on, have yet to be finalized

Opportunity for public engagement

- An opportunity to engage proactively with the public to identify their expectations and concerns
- My goal? Ultimately we want to inform how this technology will be implemented in our province in ways that accord with the very public that will use it

- 1. Public advisory council
- 2. Provincial online survey
- 3. Town hall discussions in St. John's

Step 1 – forming the public council

- Over a three month period in 2018, ads were distributed widely through professional and personal networks – there was no budget for advertising
- A council was formed from these expressions of interest and met face to face in St. John's in early June 2018
- 12 members of the public comprised the council, representing all health authorities (3 members from Labrador)

Feedback from the council

- ***Data security and access*** a key concern

Technical issues – potential the system could be 'hacked'; also included questioning where exactly the data would be housed, in what form, and for how long.

Data access – who could access stored data and test results? Who owns it?

- Data ownership was quite broad, in that Council members discussed who 'owns' the data – is it an individual patient, the Newfoundland government, the research team? Someone else entirely?
- Council members were clear that answers to these sorts of questions would be important considerations before consenting to any project.

Consent – an overarching issue

- How would it be obtained for sequencing, by whom and how often?
- Questions raised included whether consent would be obtained separately for clinical testing vs. the secondary goal of research using the stored samples
- Council members suggested an evolving consent model, recognizing that consent preferences change over time – highly endorsed patient choice and control

Suggestions to consider

- Carefully explore what potential consent models are available and feasible before offering sequencing in practice – e.g., do we have knowledgable healthcare providers who can enact consent?
- Carefully explore what kinds of secondary findings can be returned to participants and by whom. Do not offer anything to participants that ultimately won't be available
- No consensus reached on what kinds of incidental findings to return - patient choice – what to receive should be entirely up to patients
- Agreed consent should be obtained for the clinical purpose and research on the stored sample *at the same time* (recognizing that consent should be revisited in the future)

Other issues raised by the council

- Potential psychosocial impacts – good and bad, and over time (research should carefully follow those who are undergoing sequencing)
- Equity – e.g., all areas of the province should have equal access
- Need for health care provider education and training
- Need for public outreach/public launch/education campaign

Engagement through a council

- Advantages of in-depth, rich discussion
- Opportunity for ongoing engagement and sound boarding

- Disadvantage small numbers of residents
- Council was poised to contribute right away, yet decision makers were not yet in a position to implement any of their suggestions

- One of the council members and I wrote a piece about this for the BMJ's Partnership in Practice Series (https://blogs.bmj.com/bmj/2019/12/17/rolling-out-genomic-screening/)

On the council's suggestion, additional public engagement…

- Online survey in late December 2018, advertised largely over social media for two weeks
- 901 respondents answered the first question about interest in sequencing, with responses to later questions in the survey dropping (~700 answered all questions)
- Town halls in Feb 2019 in St. John's (n=20)

In terms of patient engagement…

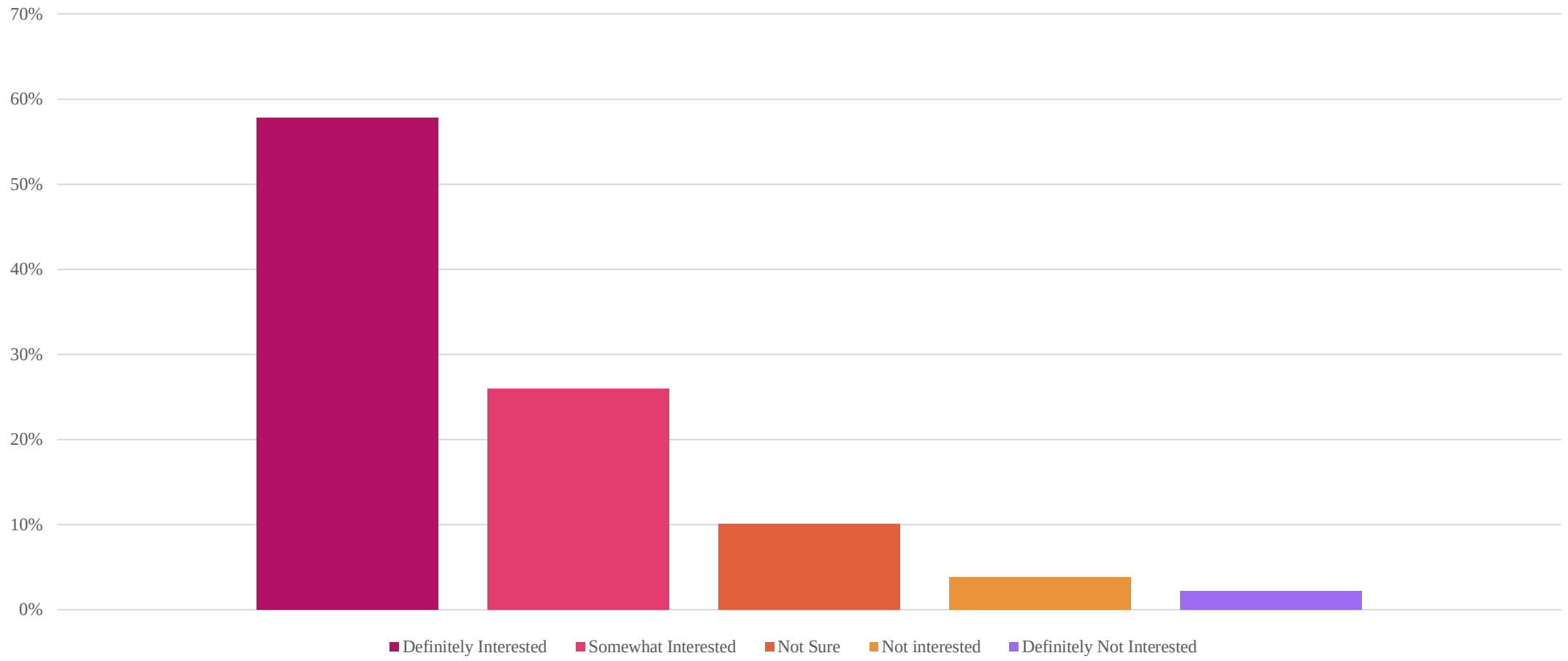
- Council members help draft the survey and were critical in revising some of the wording for a lay audience
- They reviewed a summary of results and offered input, clarification suggestions and wording tweaks
- They also reviewed the presentation used in town halls and offered suggestions for questions to be asked during the sessions

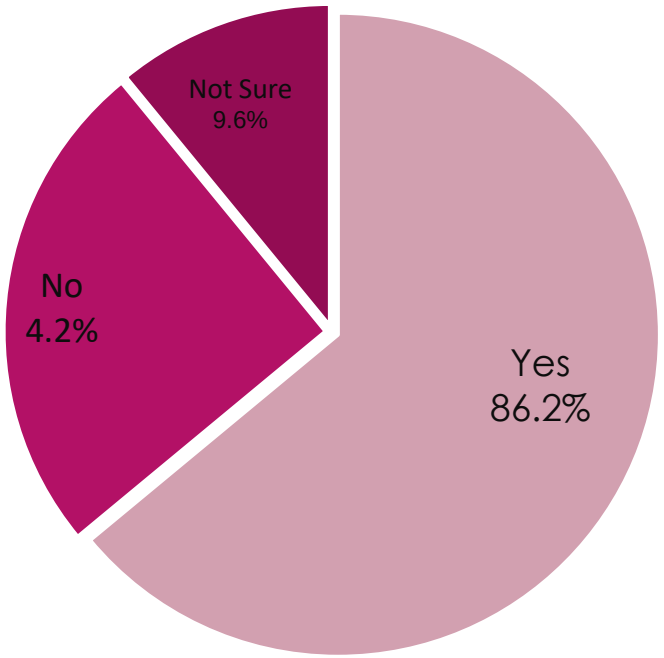
- Let's look at some results -

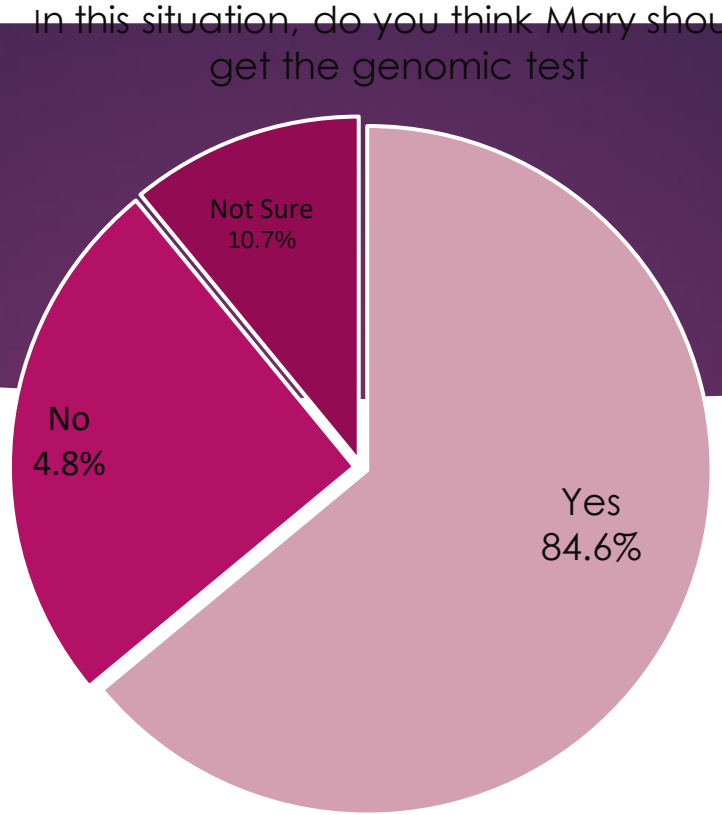
Public survey – Respondents (n=~700)

- 74.5% female
- 73.7% Urban residence
- 73.5% Eastern Health, 11.6% Central, 12.2% Western, 2.7% Labrador
- 53% University degree
- 62.9% had annual incomes over $60 000
- Most were married with children, with a mean age of 45.5 (SD 13)
- 13.3% had used direct to consumer testing

Public survey – High interest in WGS (n=901)



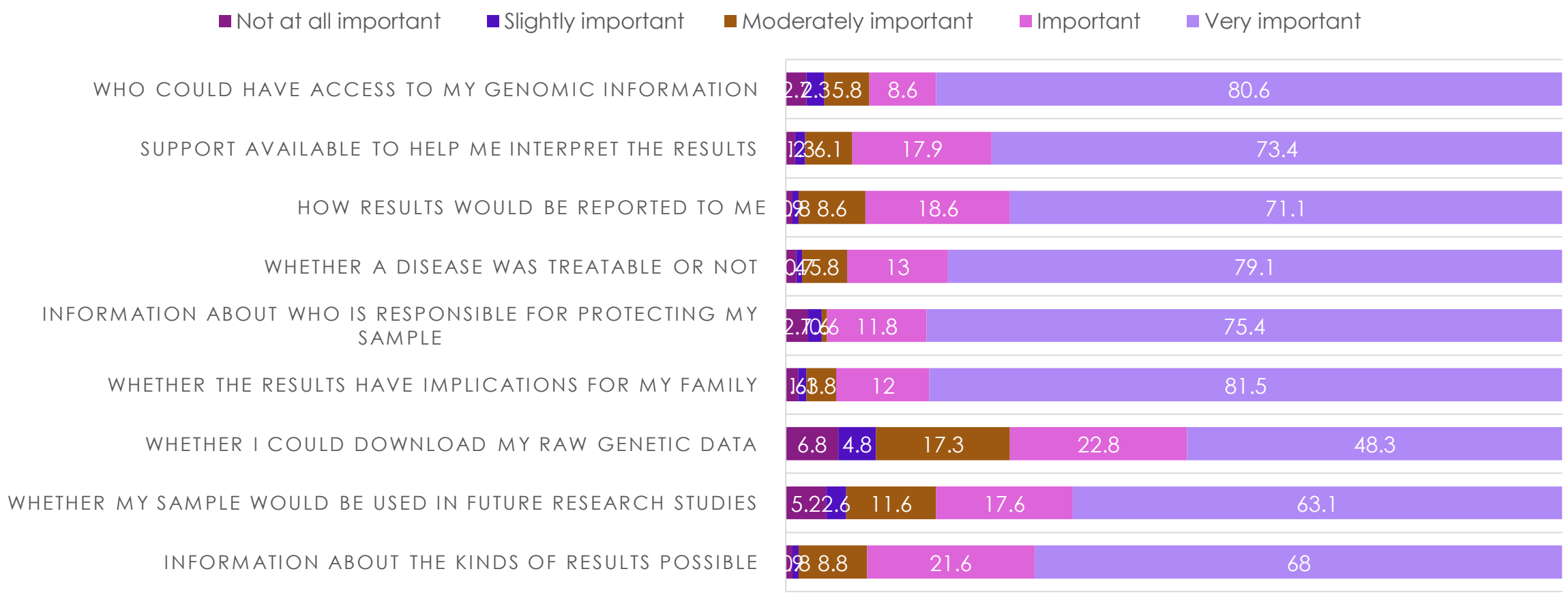




Interest in pharmacogenomic testing (n=842)

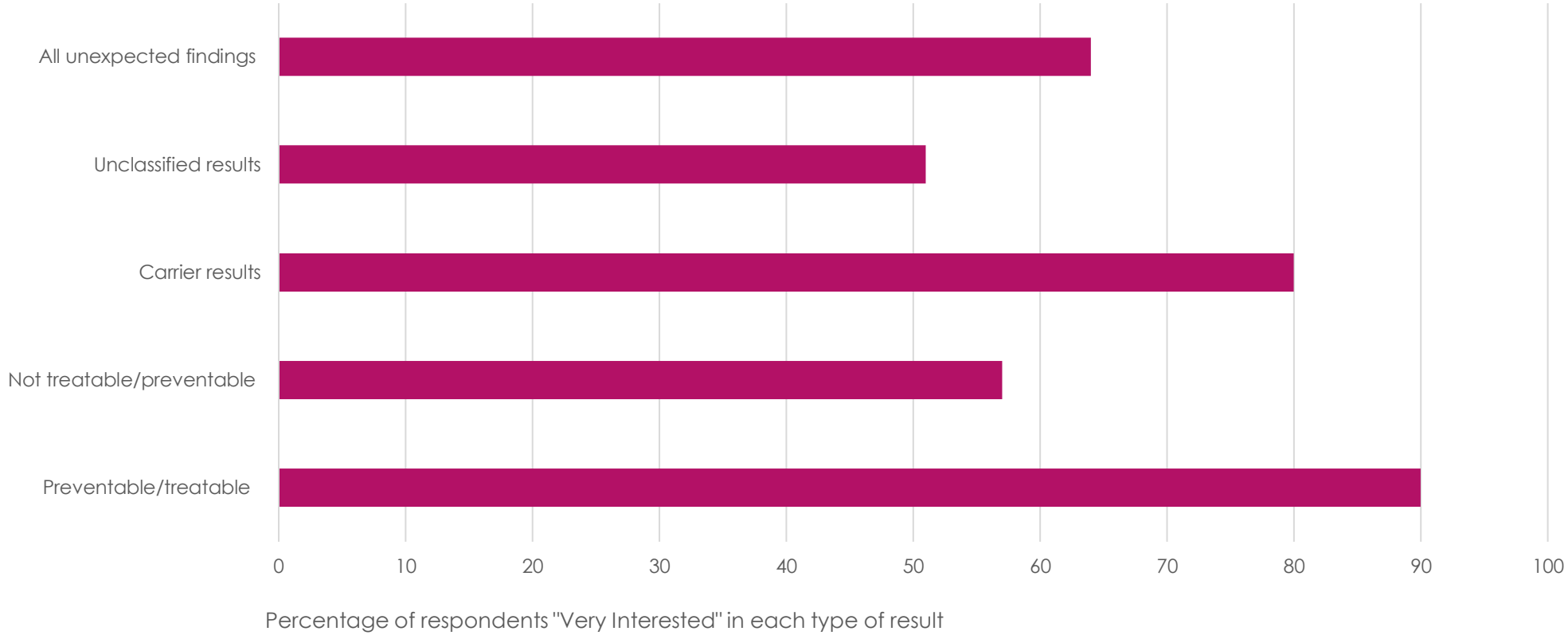
Let's consider an imaginary patient, Mary. Mary has several health problems, including diabetes and a heart valve problem. Today, she is seeing her heart specialist to talk about the possibility of needing her heart valve replaced someday. He thinks that will be necessary within five years, but if she gets sick suddenly, it could happen sooner. After her heart surgery, he tells her she will need to take a blood thinner. The heart doctor explains that he used to start all his patients on the same dose of blood thinner, and through trial and error over a few months, he would finally get the dose right. Now, however, he can do a test using whole genome sequencing that will predict how Mary's body will handle the blood thinner. He explains this will help him figure out the right dose for her faster. He would like to do the test today and record it in her medical record, so the information will be available to him when she needs it.

What info would be important?



Incidental findings? Also interested

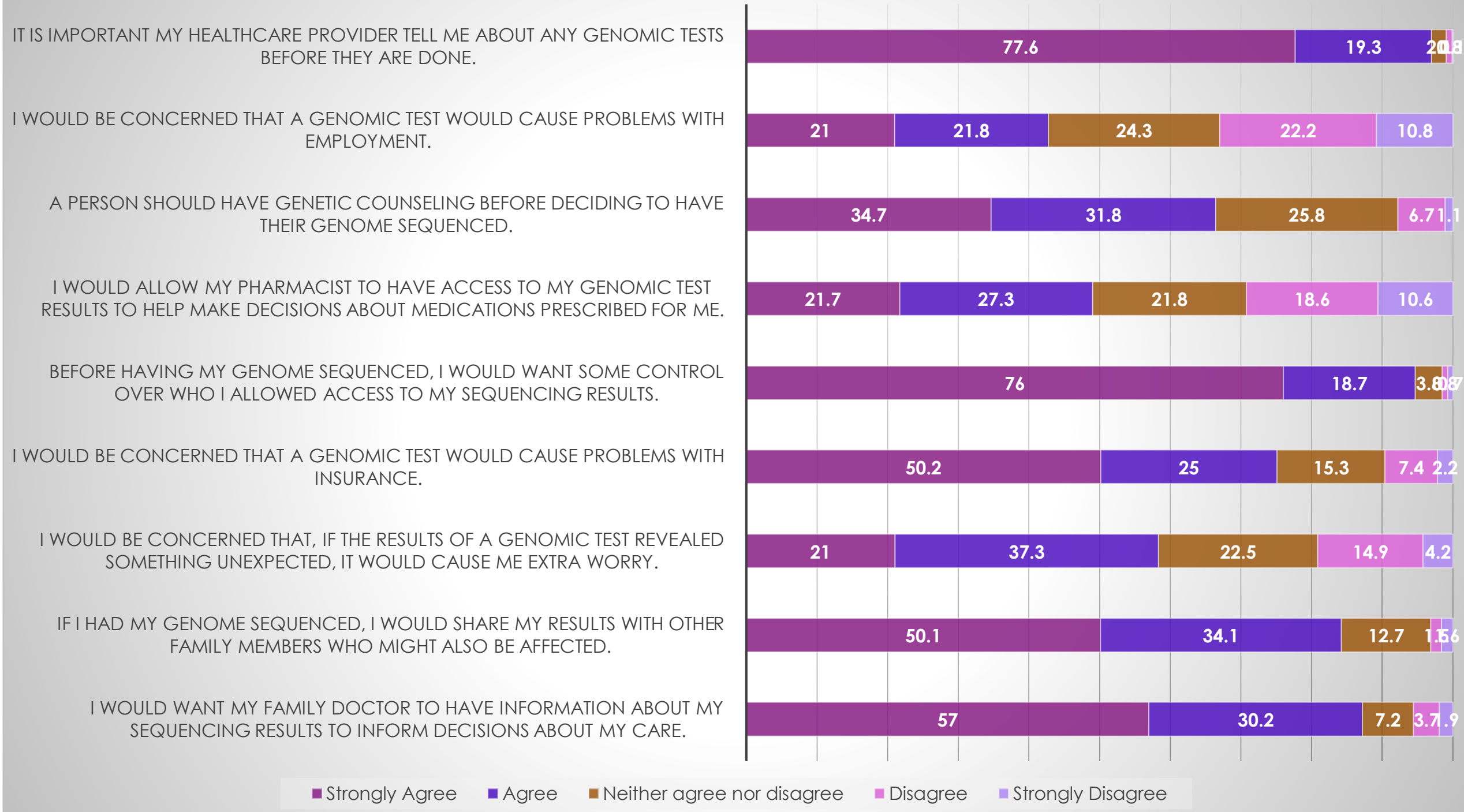
Figure 1. Preferences for learning various types of unexpected genomic findings



Attitudes towards specific features

- The next figure displays attitude statements with a Likert scale (Strongly agree to Strongly disagree

- They measure specific features of WGS and highlight respondent perceptions, expectations and concerns


IT IS IMPORTANT MY HEALTHCARE PROVIDER TELL ME ABOUT ANY GENOMIC TESTS BEFORE THEY ARE DONE.
77.6
19.3
I WOULD BE CONCERNED THAT A GENOMIC TEST WOULD CAUSE PROBLEMS WITH EMPLOYMENT.
21
21.8
24.3
22.2
10.8
A PERSON SHOULD HAVE GENETIC COUNSELING BEFORE DECIDING TO HAVE THEIR GENOME SEQUENCED.
34.7
31.8
25.8
6.7
I WOULD ALLOW MY PHARMACIST TO HAVE ACCESS TO MY GENOMIC TEST RESULTS TO HELP MAKE DECISIONS ABOUT MEDICATIONS PRESCRIBED FOR ME.
21.7
27.3
21.8
18.6
10.6
BEFORE HAVING MY GENOME SEQUENCED, I WOULD WANT SOME CONTROL OVER WHO I ALLOWED ACCESS TO MY SEQUENCING RESULTS.
76
18.7
I WOULD BE CONCERNED THAT A GENOMIC TEST WOULD CAUSE PROBLEMS WITH INSURANCE.
50.2
25
15.3
7.4
I WOULD BE CONCERNED THAT, IF THE RESULTS OF A GENOMIC TEST REVEALED SOMETHING UNEXPECTED, IT WOULD CAUSE ME EXTRA WORRY.
21
37.3
22.5
14.9
4.2
IF I HAD MY GENOME SEQUENCED, I WOULD SHARE MY RESULTS WITH OTHER FAMILY MEMBERS WHO MIGHT ALSO BE AFFECTED.
50.1
34.1
12.7
I WOULD WANT MY FAMILY DOCTOR TO HAVE INFORMATION ABOUT MY SEQUENCING RESULTS TO INFORM DECISIONS ABOUT MY CARE.
57
30.2
7.2
3.7
Strongly Agree
Agree
Neither agree nor disagree
Disagree
Strongly Disagree

Summary

- High levels of interest in whole genome sequencing and in pharmacogenomic testing specifically, despite low levels of self-reported knowledge
- Issues identified as *very important* to sequencing decisions - included familial implications of testing, whether treatment was available for conditions tested and who could access participants' genomic information
- Control and choice highlighted in attitude statements
- Findings reveal the kind of information users of sequencing services would value and should assist in the development of informed consent documents and patient education materials

Town halls

- Held in St. John's in February 2019
- Open sessions advertised widely
- Twenty members of the public took part in two town halls
- Hybrid information-consultation session – presentation about WGS and survey findings, with discussion about specific issues (e.g., consent, incidental findings, data sharing)

Town hall findings

Participants talked about what would need to be better understood before sequencing should be introduced to patients in our healthcare system

These ideas revolved around:

1) consent for sequencing, including the return of sequencing findings,
2) access to genomic data – by players both within and outside of the healthcare system, and finally
3) the need for awareness raising and education about genomics

Consent and return of findings

Consent for sequencing thought to be different on at least three fronts:

- 1. The current level of understanding of the general public about sequencing, including its varied potential implications;
- 2. The resources required to obtain consent for sequencing; and
- 3. What kinds of results to return to participants and how to obtain consent for these

Quotes – Consent, resources, implications of testing

It's different to go in and get bloodwork done to test for high cholesterol vs. genomic sequencing. Most people won't understand the implications of getting your genome sequenced… –Town Hall 2

And what about the resources required to obtain consent? Right now if things are done in a research protocol, there is a strict protocol and time to explain. But the time required for this in healthcare would have huge resource implications. –Town hall 2

Cost – can we afford to do this? Genetic testing is very limited already. How will it affect healthcare resources – e.g., patients demanding investigative tests? -Post session survey

What about the impact on other family members who may not have provided consent or may not want to know about the findings? –Participant, town hall 1

Returning results

You need someone to interpret it and explain it to the patient. For example, finding out you have Huntington's or Alzheimer's – a patient might die of fright from finding out the potential to have the condition vs. the actual condition. It's easy for the public to misinterpret information – even when we think we want it all back. –Participant, town hall 1

Returning results – flip chart exchange

"People need to be told upfront – here are the possible results, tell us what information you need or results you want. It could be framed as:

Results could come back here that may cause you worry; some of these disorders could affect your children; some are not treatable, etc. These are the types of results possible (insert check boxes):

- Information about conditions that are treatable (for you and your children)
- Information about disorders that are not treatable
- Information that we really don't know what it means yet

People could then select the types of results they are interested in. Maybe include a question or statement for self-reflection – e.g., the information you receive may affect your quality of life because what we think right now in this moment may not be the case 10 years down the road".

Access – healthcare system and beyond

- "*Pharmacists already have access to our medications, so it wouldn't be too much of a leap to access pharmacogenomic results.*"
- However, it was noted that participants wouldn't want other people working in pharmacies beyond their pharmacist (e.g., reception staff) to have access to all their genomic data.

When you think about genetic testing, you think about how this will affect my children or grandchildren. What are the ripple effects on employment opportunities, insurance, travel, etc. –Participant, town hall 2

There may be cases where people don't want to know that a sibling of theirs is not really a sibling. Who outside the medical community is going to have access to this information? Who can request this information, maybe through legal channels? – Participant, town hall 1

Education needed – for all

- Participants suggested that a general public awareness campaign could assist in building awareness about sequencing, including its risks and benefits, before a healthcare provider ever offered it to patients.

This needs to happen before people enter a clinician's office so they are not ambushed with too much information during an appointment – good, general public education. –Participant, town hall 1

A simple video to inform on the basics of sequencing, showcase its implications, etc. –Post session survey

Summing up

- All findings correspond fairly well with the literature
- Respondents grappled with the same issues decision makers do – governance, consent and return of results policies, how to prepare both publics and providers for genomic medicine
- Public very willing to engage in these discussions and offer specific suggestions
- Paying attention to the issues that are of importance to the public should very tangibly guide the creation of informed consent documents, patient education material, as well as policy development

Acknowledgements

- Thank you also to the public advisory council who helped create the survey and town hall protocols and gave generously of their time
- Grateful to provincial medical genetics staff who also reviewed the survey and offered excellent feedback
- Many thanks to the research team -
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Papers from this work

- Abhyankar S, Etchegary H. Rolling out genomic screening. The Newfoundland and Labrador Public Advisory Council on Genomics (PACG). *BMJ Partnership in Practice* 2019; 12(17): https://blogs.bmj.com/bmj/2019/12/17/rolling-out-genomic-screening/
- Etchegary H, Wilson B, Rahman P, Simmonds C, Pullman D. Public interest in whole genome sequencing and information needs: An online survey study. *Personalized Medicine*. Online first, June 2020; doi: https://doi.org/10.2217/pme-2019-0136
- Etchegary H, Winsor M, Power A, Simmonds C. Public engagement with genomic medicine: A summary of town hall discussions. *J Community Genet* Online first, August 2020 https://doi.org/10.1007/s12687-020-00485-1

Questions?

- Contact me holly.etchegary@med.mun.ca