Using genomics to identify new causes of cancer: a global context

Paul Brennan

International Agency for Research on Cancer
Lyon, France
About 40% of cancers can be explained by known risk factors

Parkin DM et al, BJ C 2011

Many causes of cancer remain to be discovered

International Agency for Research on Cancer

World Health Organization

Let’s beat cancer sooner

cruk.org/health
WCRF third report

OUR CANCER PREVENTION RECOMMENDATIONS

- Limit consumption of red and processed meat
- Limit consumption of sugar-sweetened drinks
- Limit alcohol consumption
- Do not use supplements for cancer prevention
- For mothers: breastfeed your baby, if you can
- After a cancer diagnosis: follow our recommendations, if you can

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk. Following these recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

wcrf.org
WCRF third report

Around 42% of all cancers are preventable
WCRF third report

Around 42% of all cancers are preventable…
…based on current knowledge
What about the other 60%?
What about the other 60%?
What about the other 60%?

It's not chance!
Large international differences cannot be chance

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Low incidence region</th>
<th>Incidence rate/ 100.000 (mortality)</th>
<th>High incidence region</th>
<th>Incidence rate/ 100.000 (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Vietnam</td>
<td>3.2 (1.8)</td>
<td>Ireland</td>
<td>126 (17.9)</td>
</tr>
<tr>
<td>Brain</td>
<td>Singapore</td>
<td>1.8 (1.3)</td>
<td>US</td>
<td>6.3 (3.6)</td>
</tr>
<tr>
<td>Testes</td>
<td>South Korea</td>
<td>0.7 (0.1)</td>
<td>Norway</td>
<td>12.1 (0.2)</td>
</tr>
<tr>
<td>NHL</td>
<td>Vietnam</td>
<td>1.7 (1.2)</td>
<td>US</td>
<td>16.3 (4.0)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Thailand</td>
<td>1.7 (1.0)</td>
<td>Czech Rep</td>
<td>23.6 (8.3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>India</td>
<td>1.1 (1.0)</td>
<td>Japan</td>
<td>10.0 (9.0)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Gambia</td>
<td>2.2 (2.0)</td>
<td>Japan</td>
<td>41 (15.2)</td>
</tr>
</tbody>
</table>
How can genomics reveal new causes of cancer?

1. The cancer genome
   - mutation signatures

2. Our own germline variation
   - Mendelian randomization
How epidemiology works

exposure → cancer

Confounders and biases...
How epidemiology works

Body weight → Cancer

Diet
- Socioeconomic status
- Hypertension
- Physical activity...

Various biases
Mendelian randomization:
Use genes for an exposure/ not the exposure itself

Genes that influence body weight

Cancer

Socioeconomic status
Hypertension
Physical activity...

Various biases
Social deprivation and BMI among 500,000 UK adults

BMI

Increasing social deprivation

More deprived
Social deprivation and BMI among 500,000 UK adults

More deprived

Increasing social deprivation

Genetic score of BMI

UK Biobank
Effect of 5 BMI unit increase on cancer risk
WCRF third report v Mendelian randomization analysis

Pancreatic Cancer

Relative Risk

WCRF 3rd Report

1.10
Effect of 5 BMI unit increase on cancer risk
WCRF third report v Mendelian randomization analysis

Pancreatic Cancer

WCRF 3rd Report
MR analysis*

Relative Risk
1 1.5 2

1.10 1.47
Effect of 5 BMI unit increase on cancer risk
WCRF third report v Mendelian randomization analysis

Pancreatic Cancer

WCRF 3rd Report
MR analysis*

*Weighted measure of 700 gene variants found to be associated with BMI
Effect of 5 BMI unit increase on cancer risk

WCRF third report v Mendelian randomization analysis

Cancer Sites
- Pancreas: 1.10
- Colorectum: 1.05
- Kidney: 1.30
- Endometrium: 1.50
- Ovary: 1.06
- Esophagus (Adeno): 1.48
- Head and Neck: 1.15

Relative Risk
Effect of 5 BMI unit increase on cancer risk

WCRF third report v Mendelian randomization analysis

<table>
<thead>
<tr>
<th>Cancer Sites</th>
<th>WCRF 3rd Report</th>
<th>MR analysis *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>1.10</td>
<td>1.47</td>
</tr>
<tr>
<td>Colorectum</td>
<td>1.05</td>
<td>1.44</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.30</td>
<td>1.59</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1.50</td>
<td>2.06</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.06</td>
<td>1.13</td>
</tr>
<tr>
<td>Esophagus (Adeno)</td>
<td>1.48</td>
<td>2.10</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>1.15</td>
<td>1.15</td>
</tr>
</tbody>
</table>
Effect of 5 BMI unit increase on cancer risk
WCRF third report v Mendelian randomization analysis

Cancer Sites

Breast (postmenopause)

Lung

WCRF 3rd Report  MR analysis *

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>WCRF 3rd Report</th>
<th>MR analysis *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (postmenopause)</td>
<td>1.12</td>
<td>0.57</td>
</tr>
<tr>
<td>Lung</td>
<td>0.89</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Relative Risk

0.5  1  1.5
• Genetic analysis among over 400,000 individuals

• ‘Higher levels of obesity increase the risk of individuals taking up smoking, as well as smoking intensity’.
Many potential uses of Mendelian randomization for cancer

- **Anthropometric** - BMI, etc
- **Behavior**: smoking, alcohol consumption, coffee consumption
- **Clinical conditions**, e.g. diabetes, insulin levels, lipids, hypertension, lung function etc
- **Circulating vitamins**, e.g. vitamin D, Vitamin B6, folate, B12…
- **Circulating metabolites and proteins**, 
- **Drug targets**….e.g PCSK9 inhibitors

- Can look at the effect on disease outcome as well as onset
Increased fasting insulin levels and cancer risk: a Mendelian randomization analysis

Cancer Sites | MR
---|---
Lung | 1.48
Pancreas | 1.66
Kidney | 1.82

Relative Risk

Summary

- Genetics is playing an increasing and important contribution to our knowledge of the causes of cancer
Summary

• Genetics is playing an increasing and important contribution to our knowledge of the causes of cancer
• This evidence is complimentary to other forms of evidence
Summary

• Genetics is playing an increasing and important contribution to our knowledge of the causes of cancer
• This evidence is complimentary to other forms of evidence
• It has important potential to help fill in the missing 60%
Summary

• Genetics is playing an increasing and important contribution to our knowledge of the causes of cancer
• This evidence is complimentary to other forms of evidence
• It has important potential to help fill in the missing 60%
• Lots more to come......
Acknowledgements

International Agency for Research on Cancer (Lyon, France)
• Daniela Mariosa
• Robert Carreras-Torres
• Valérie Gaborieau
• Mattias Johansson

MRC Integrative Epidemiology Unit (Bristol, UK)
Dr George Davey Smith
Dr Richard Martin
Dr Caroline Relton
Dr Philip Haycock

Funding:
CRUK “Reducing the burden of cancer” (PI: R Martin & C Relton)
Bridging the cancer genetics divide:

Considerations for low and middle income countries

Ophira Ginsburg MSc MD
High-Risk Cancer Genetics Program, Perlmutter Cancer Center
Section for Global Health, Department of Population Health
NYU Langone Health

Disclosure of interest: None declared
Objectives:

- To have a basic understanding of the common hereditary cancer syndromes, and to be aware of rapidly changing evidence-informed guidelines for testing and clinical management.

- To know the concepts of multigene panels, tumor/normal sequencing (NGS), and the expanding and critical role(s) of well-trained providers such as the cancer genetic counselor.

- To consider what core elements are needed to ensure that a cancer genetics service can provide high quality comprehensive patient care, that is “reasonable” for a given context and health system.
BRCA 1 Family

Frequency:
- General population: 1/500-1/700
- Ashkenazi Jewish: 1/40

LEGEND
- Breast cancer
- Ovarian cancer

Pedigree modified to protect confidentiality
Lynch Syndrome

- CRC dx 45
- CRC dx 61
- CRC dx 75
- Ovarian Ca, dx 64
- CRC dx 48
- CRC dx 52
- Endometrial Ca, dx 59
- 45
- CRC dx 42
DNA Sequencing

Sanger Sequencing
Gold standard since 1970s

Two reads per DNA position
Used for single gene testing and confirmatory testing

Next-Generation Sequencing
Clinically available in 2010

Simultaneous reading for each targeted position
Used for multi-gene testing and high throughput data
Cost effective for more than one gene analyzed

New Frontiers...germline testing for risk prediction/reduction.... treatment

Myriad files for patent on BRCA1

BRCA1 isolated
BRCA2 isolated

Preclinical data on PARP inhibitors

Olaparib Phase I
Olaparib Phase II
Olaparib halted

Olaparib Phase III
FDA approves olaparib

Exclusive patent rights to Myriad Genetics

HR genes and hereditary cancer risk recognized

Supreme Court Ruling against Myriad patents
Gene panel testing starts

FDA approves BRACAnalysis CDx™

2015- patients tested before 8/2015 are eligible for update panel testing at Myriad

Modified from Walsh, 2015
“Multigene testing is ideally ordered in the context of professional genetic expertise for pre- and post-test counseling.... for risk prediction, risk reduction for patient & family members, tailored TREATMENT options”

NCCN 2018....
### Hereditary Cancer Multigene Panels

<table>
<thead>
<tr>
<th></th>
<th>BRC Aplus 8 genes</th>
<th>BreastNext 17 genes</th>
<th>GYNplus 13 genes</th>
<th>OvaNext 25 genes</th>
<th>ColoNext 13 genes</th>
<th>ProstNext 14 genes</th>
<th>PancNext 13 genes</th>
<th>CancerNext 34 genes</th>
<th>BrainTumorNext 27 genes</th>
<th>MelanomaNext 19 genes</th>
<th>RenalNext 17 genes</th>
<th>PG L Next 17 genes</th>
<th>CancerNext 67 genes</th>
<th>CustomNext-Cancer up to 81 genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARD1</td>
<td>BARD1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>BRIP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRE1A</td>
<td>MRE1A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>NBN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>NF1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD50</td>
<td>RAD50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>RAD51C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>RAD51D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>ATM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>PALB2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td>MUTYH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>CHEK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>CDH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>BRCA1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>BRCA2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>PTEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>TP53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>MLH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>MSH2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>MSH6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>PMS2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPCAM</td>
<td>EPCAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMARCA4</td>
<td>SMARCA4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>APC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMPRIA</td>
<td>BMPRIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td>SMAD4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A</td>
<td>CDKN2A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM1</td>
<td>GEM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLE</td>
<td>POLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOXBN</td>
<td>HOXBN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DICER1</td>
<td>DICER1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDK4</td>
<td>CDK4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GREM1</td>
<td>GREM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLQ</td>
<td>POLQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLEX1</td>
<td>DLEX1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CRITERIA FOR FURTHER GENETIC RISK EVALUATION

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing.
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing (see BRIVO.A.3 of 3).
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER, PR, HER2+) breast cancer diagnosed age ≤50 y
  - Two breast cancer primaries
  - Breast cancer at any age, and
  - ≥2 close blood relatives with:
    - breast cancer age ≤50 y; or
    - invasive ovarian cancer; or
    - male breast cancer; or
    - pancreatic cancer; or
    - high-grade (Gleason score ≥7) or metastatic prostate cancer

Consider referral to cancer genetics professional.

See Assessment (BRIVO.2).

Note: All recommendations are Category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered (i.e., pre-test counseling) and after results are disclosed (i.e., post-test counseling). A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in the counseling of patients.

Pre-test counseling includes:
- Collection of a comprehensive family history
  - Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family. See BRI/OD/A3.
  - Evaluation of a patient’s cancer risk
  - Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity
  - Preparing the patient for possible outcomes of testing including positive (pathogenic, likely pathogenic), negative, and uncertain findings and obtaining informed consent

Post-test counseling includes discussions of:
- Results along with their significance and impact and recommended medical management options
- Interpretation of results in context of personal and family history of cancer
- Informing and testing at-risk family members
- Available resources such as disease-specific support groups and research studies

Genetic Testing Considerations
- Testing should be considered in appropriate high-risk individuals where it will impact the medical management of the tested individual and/or their at-risk family members. It should be performed in a setting in which it can be adequately interpreted.
- The probability of pathogenic/likely pathogenic variant detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial pathogenic/likely pathogenic variant detection. The estimated likelihood of pathogenic/likely pathogenic variant detection may be very low in families with a large number of unaffected female relatives.
- Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA until other technologies are available. If available, DNA should be extracted from a fibrobial culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.
- Comprehensive genetic testing includes full sequencing and testing for large genomic rearrangements. It is encouraged that testing be done in commercial or academic labs that are clinically approved and validated. See BRI/OD/A3 of 3.
- In children <18 y, genetic testing is generally not recommended when results would not impact medical management.
- Likely pathogenic variants are often treated similarly to pathogenic variants.
American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

Mark E. Robson, Angela R. Bradbury, Banu Arun, Susan M. Domchek, James M. Ford, Heather L. Hampel, Stephen M. Lipkin, Sapna Syngal, Dana S. Wollins, and Noralane M. Lindor
3 technical considerations for policymakers:

- Analytical validity (NB/ high rates of discordance btw commercial labs)
- Clinical validity (reliable evidence of strength of association)
- Clinical utility (proven / evidence for the information leading to prevention/screening or Rx that impacts health – not always clear)

accompanying editorial:

“New technology is introducing great complexity”

#understatementoftheyear
Genetic Testing for Breast Cancer in the Era of Multigene Panels: Can We Make an Impact on Population Health?

Ophira Ginsburg, Perlmutter Cancer Center NYU Langone Health, New York, NY
Paul Brennan, International Agency for Research on Cancer, Lyon, France

See accompanying article doi:https://doi.org/10.1200/JCO.2018.78.3977
Technical, regulatory, and health systems considerations

1. What is understood about the acceptability of genetic testing for hereditary cancer in a community? (stigma about cancer, about hereditary disease)

2. Does “testing” include comprehensive education and post-test counseling by trained providers? (many ordering providers in U.S. get this wrong!)

JCO 2018 Ginsburg and Brennan
Technical, regulatory, and health systems considerations

3. Who will interpret variants of uncertain significance? (can be very complicated)

4. Work force and technical capacities for risk-reduction interventions? (if access to timely, affordable, good quality diagnostic imaging, pathology, screening, and surgery is limited, why offer testing?)

JCO 2018 Ginsburg and Brennan
Technical, regulatory, and health systems considerations

5. Have ethical, legal, and regulatory frameworks to protect personal and to protect individuals from genetic discrimination? (“GINA” like legislation?)

6. Is the health system funded well enough to support cancer genetics services? (what % GDP is spent on health? Public/private?)
Questions?

Thank you!
Are we ready for population-wide germline genetic testing? An example from Brazil

Patricia Ashton Prolla, MD, PhD
pprolla@hcpa.edu.br

Hospital de Clínicas de Porto Alegre, Brazil
Universidade Federal do Rio Grande do Sul, Brazil
Rede Brasileira de Câncer Hereditário

• Track 2: Advances in screening and early detection
Objectives

- To review the basic epidemiology of breast cancer in Brazil and fundamentals of hereditary breast cancer;

- To review statistics of a founder \textit{TP53} germline mutation, R337H, in Southern Brazil and its role in breast cancer predisposition;

- To consider pros and cons of population testing for R337H and what questions must be answered in order to enable adequate testing and management of mutation carriers in the long term.
Estimated age-standardized incidence rates (World) in 2018, breast, all ages

https://gco.iarc.fr
Breast Cancer in Latin America and Brazil

- Most common cancer in women;
- 59,700 new breast cancer cases are estimated in 2018;
- Adjusted incidence rates
  - Entire country: 51.33/100,000
  - South region: 73.07/100,000

_Lancet Oncol_ 2013; 14: 391-436

A. Mortality-to-incidence ratios by cancer type

- Latin America
- Japan
- European Union
- USA
At least 10% of all Breast Cancers are Hereditary

**Penetrance:** moderate - high; germline mutations cause a well known cancer syndrome.

**Allele frequency:** very low - low.

**OR for breast cancer:** > 5.0.

**Actionability:** high; evidence based risk reducing guidelines exist.

**Implications for other family members:** well defined.
Genetic Heterogeneity of Hereditary Breast Cancer: Multigene Panel Testing

<table>
<thead>
<tr>
<th>GENE</th>
<th>N</th>
<th>% of all Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>12</td>
<td>17.4</td>
</tr>
<tr>
<td>BRCA1</td>
<td>7</td>
<td>10.1</td>
</tr>
<tr>
<td>PALB2</td>
<td>7</td>
<td>10.1</td>
</tr>
<tr>
<td>MUTYH&lt;sup&gt;po&lt;/sup&gt;</td>
<td>6</td>
<td>8.7</td>
</tr>
<tr>
<td>ATM</td>
<td>6</td>
<td>8.7</td>
</tr>
<tr>
<td>BRCA2</td>
<td>5</td>
<td>7.2</td>
</tr>
<tr>
<td>PMS2</td>
<td>5</td>
<td>7.2</td>
</tr>
<tr>
<td>NBN</td>
<td>4</td>
<td>5.8</td>
</tr>
<tr>
<td>BRIP1</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>p53</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>APC</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>MSH6</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>MRE11A</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>NF1</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>CDH1</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>RAD50</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>RAD51D</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>BARD1</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

VUS [n=168*; 42%]

Uninformative [n=157; 39%]

Positive [n=69*; 17%]

Inconclusive (n=9; 2%)

Slavin et al. 2015
Best genetic testing approach: high risk testing vs. population testing?
Southern Brazilian Founder Mutation

*TP53* c. 1010G>A (p.Arg337His)

About 1:300 newborns in Southern Brazil carry *TP53* R337H

Adrenocortical carcinoma screening offered until age 15 ys
Wilson & Jungner Criteria for Newborn Screening (1968): applied to TP53 R337H

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Condition to be screened should be a significant health problem</th>
<th>The natural history of the condition should be well known</th>
<th>Condition should have a detectable preclinical phase</th>
<th>Early detection should be beneficial compared with late detection</th>
<th>An appropriate test should be available for application during the early phase</th>
<th>Test must follow an accepted procedure</th>
<th>Benefits must outweigh physical and psychological risks</th>
<th>Costs must be modest compared with benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>


**TP53 mutations and breast cancer in Brazil**

Pathogenic/Likely Pathogenic variants in 1554 hereditary breast cancer patients in Brazil (Multigene panel testing)

Most (70%) are R337H

Guindalini RS et al, unpublished
TP53 c. 1010G>A (p.Arg337His) and Breast Cancer in Southern Brazil

303 consecutively recruited breast cancer patients (age at diagnosis <50) from an outpatient breast surgery clinic

40 with modified Chompret criteria
1 carrier (2.5%)

263 without modified Chompret criteria
6 carriers (2.3%)

1/43 early onset BC patients in this series is an R337H carrier; Chompret criteria for TP53 testing are insufficient to detect most carriers.

Camila Bittar, preliminary results, unpublished
Should all women with early onset breast cancer in Southern Brazil be tested for R337H?

Why not?
Mutation frequency is high and criteria-based testing will likely miss most carriers.

And what about population screening in asymptomatic individuals?
Frequency of Thyroid Carcinoma in Brazilian TP53 p.R337H Carriers With Li Fraumeni Syndrome

In conclusion

✓ Approach for TP53 R337H mutation testing in Brazil must be urgently reviewed.

✓ Best setting? pre-menopausal breast cancer patients ("diagnostic")
  NB screening; asymptomatic young adults ("predictive")

✓ Unanswered questions that must be addressed for successful long-term outcomes:
  - Prevalence of the mutation in the population (all 5 regions) ?
  - Penetrance (Breast cancer; who will get pediatric/adult onset cancers) ?
  - Feasibility of population-wide testing, counseling and screening of carriers, including acceptance within the population.
Thank you!