



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center

NCI

Comprehensive
Cancer Center

A Cancer Center Designated by the
National Cancer Institute

Personal Perspectives on Henry Lynch and Future Directions in Preventive Oncology

Patrick Lynch, JD, MD
Professor of Medicine
UT MDACC
19 April 2020



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

Disclosures

- **Scientific advisory panel for SLA Pharma and CPP Pharma**
- **Clinical trial support from CPP Pharma**



AT THE FOREFRONT

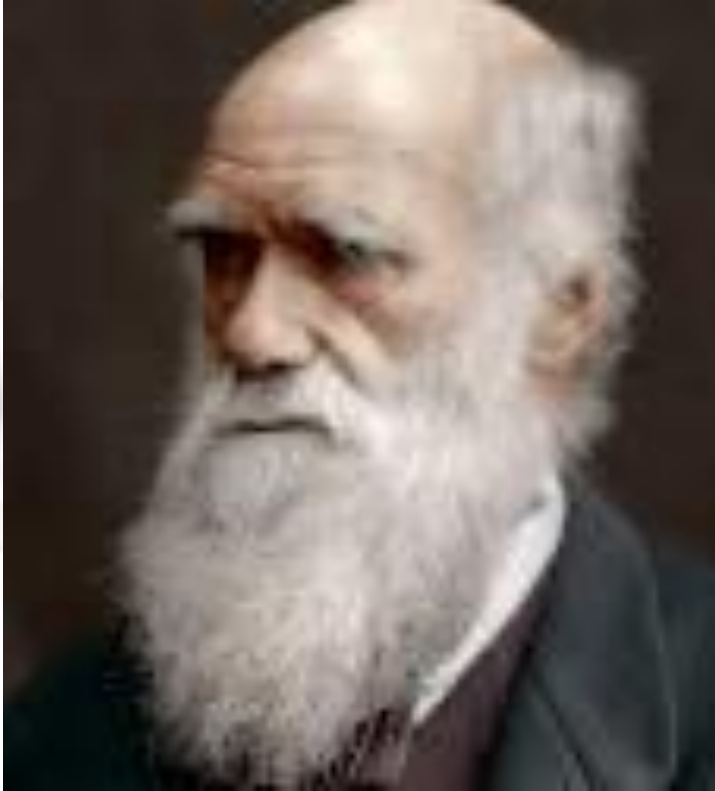
UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

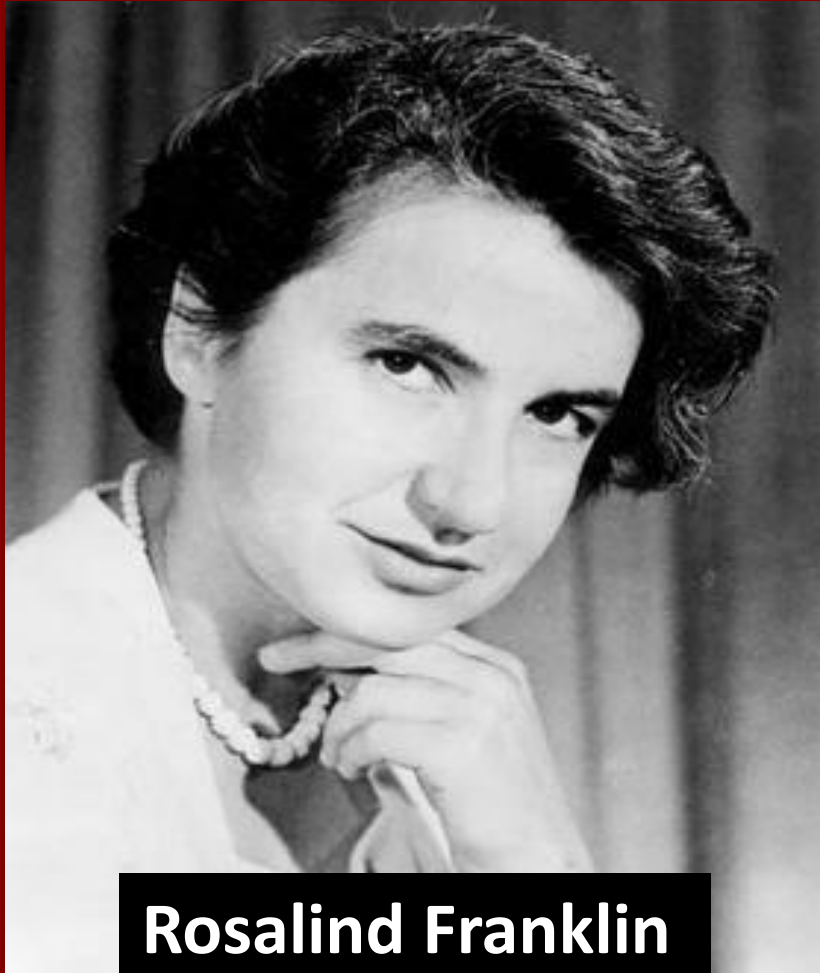
UChicago Medicine

Comprehensive Cancer Center

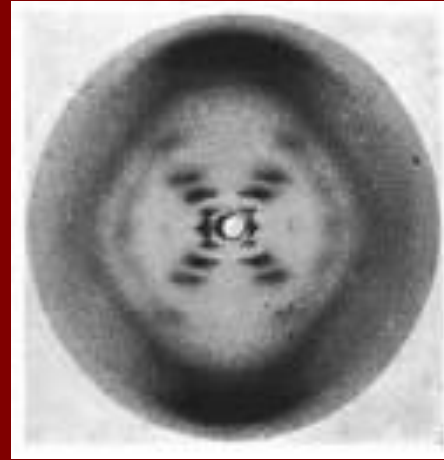
NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute



Rosalind Franklin
1920-1958



The more I learned about Franklin, the more I understood that the connection between us was stronger than I had imagined. Franklin was of Eastern European Jewish descent and she, too, had a family history of cancer. Like me, and my grandmother before me, Rosalind was diagnosed with cancer at a young age. Like my grandmother, she died young of this dreaded disease. Franklin was only 37 when she lost her battle with ovarian cancer.

Sue Friedman



AT THE FOREFRONT

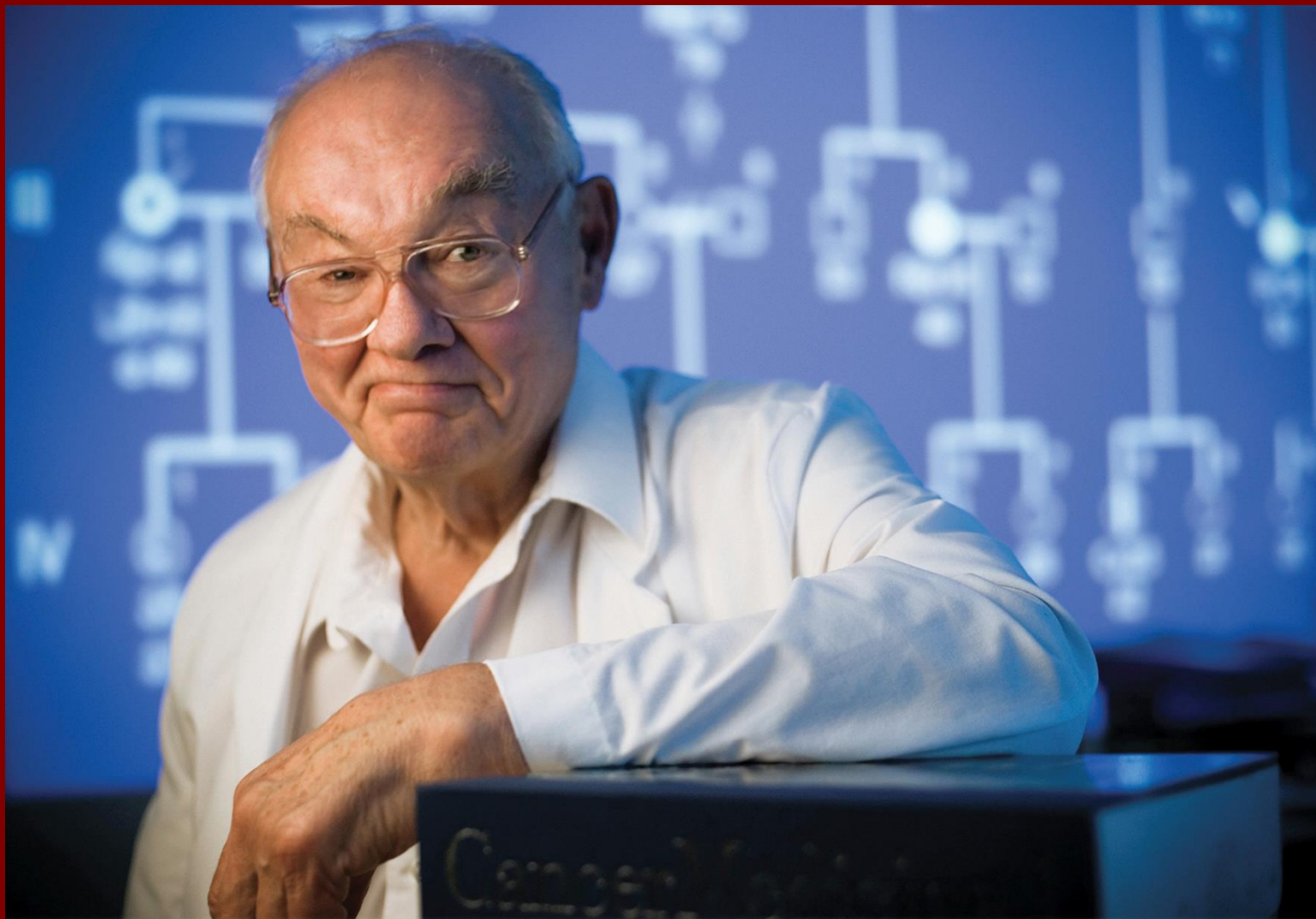
UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute



Mass>>NY>US navy>west>>>Tx>>>>Neb

1928 30's '44-45 40's-50 '50-'60 60's-2019



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute



Dr. Aldred Scott WARTHIN

(1866-1931)

HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL
LABORATORY OF THE UNIVERSITY OF MICHIGAN,
1895-1913 *

ALDRED SCOTT WARTHIN, M.D.

ANN ARBOR, MICH.



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

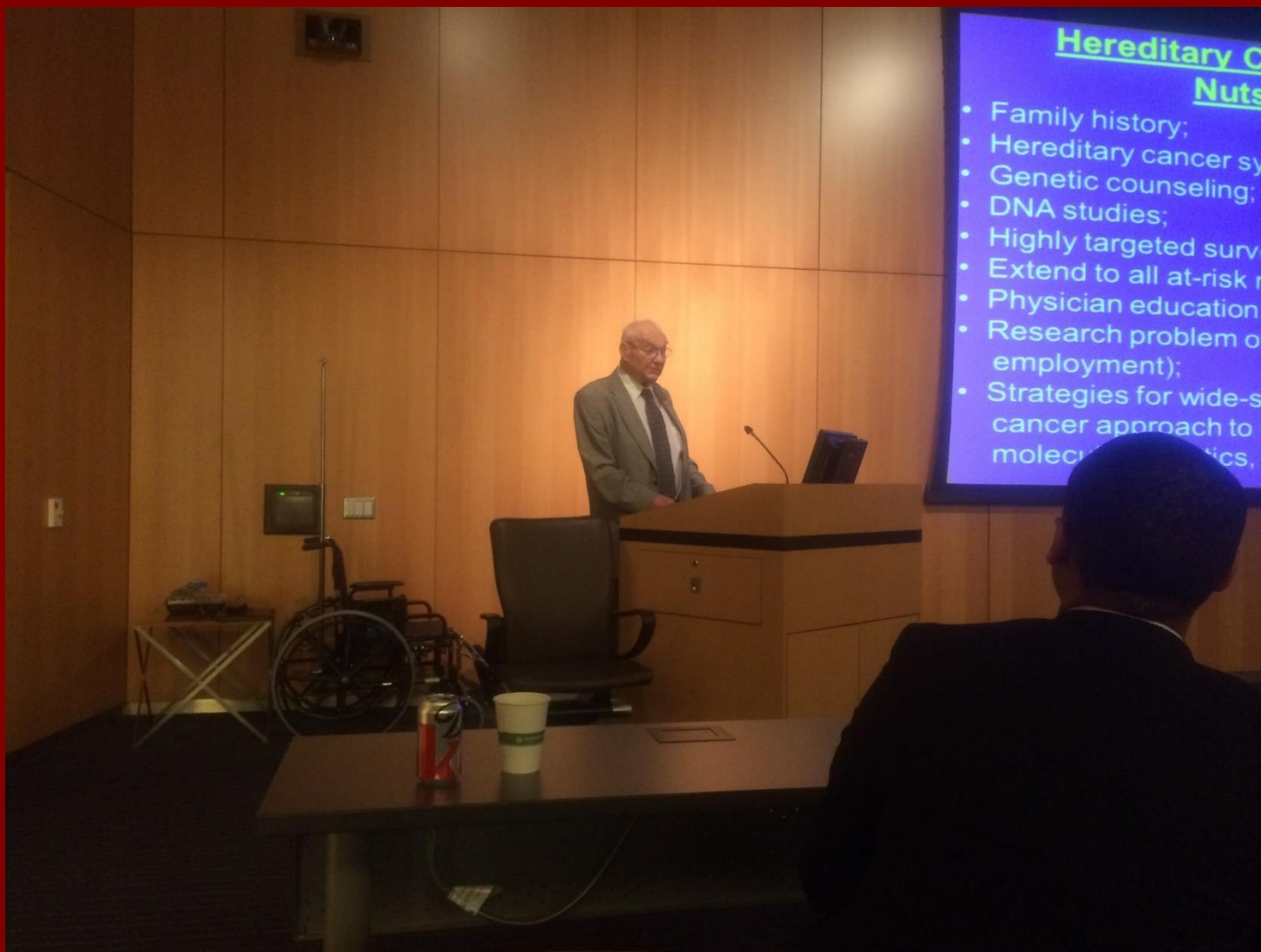
UChicago Medicine

Comprehensive Cancer Center

NCI

Comprehensive
Cancer Center

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

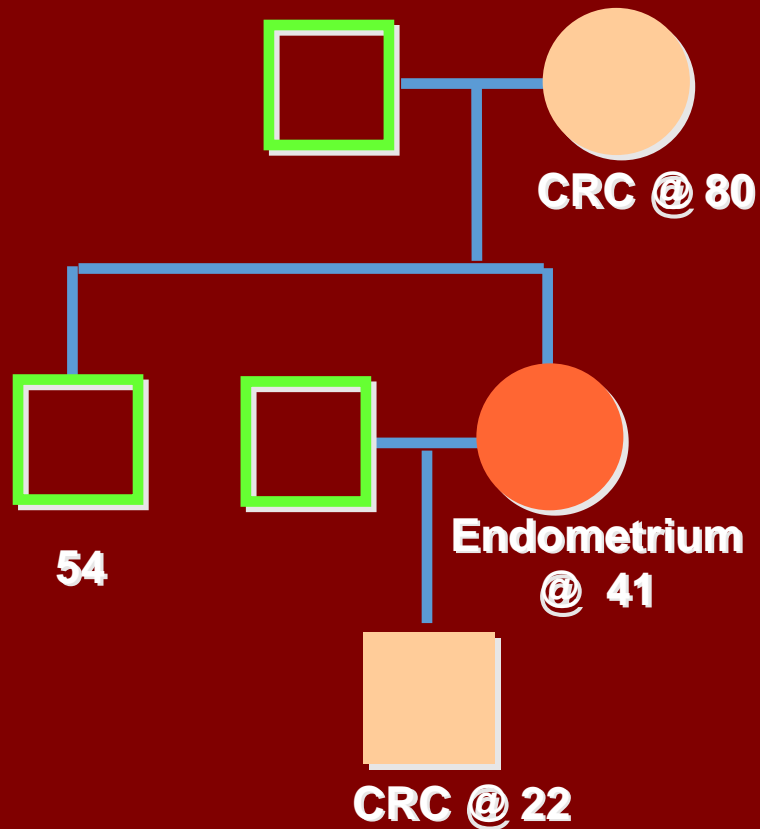
UChicago Medicine

Comprehensive Cancer Center



Comprehensive
Cancer Center

A Cancer Center Designated by the
National Cancer Institute



Amsterdam Criteria II

- 3 or more CRC (or *HNPCC-associated tumors*)
- 2 or more generations
- 1 affected age by 50, 1 case a 1^o relative of the other two
- Attenuated FAP excluded



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

**Comprehensive
Cancer Center**

A Cancer Center Designated by the
National Cancer Institute





AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute



Time has been very kind to Henry; so many of his predictions have been confirmed

What were once thought to be casual anecdotes from frightened families ended up being the substrate for some of the most important discoveries of the twentieth century

Boland: Gastro '19; 157:905



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

Comprehensive
Cancer Center

A Cancer Center Designated by the
National Cancer Institute

Cancer Prevention In Genetic Syndromes



"I'll have an ounce of prevention."



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

**The place for risk-reducing surgery clearly
established in BRCA, FAP, HNPCC, MEN...**

**Medical approaches-“chemoprevention” less
well settled, as trials very difficult, results mixed**



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

BRCA Carriers

**Discuss option of risk-reducing mastectomy
RRSO at 35-40 after child-bearing complete
(40-45 in BRCA2)**

Tamoxifen lowers risk (with if's, and's, but's)

Possible role for aromatase inhibitors

PGD considered (w cautionary comments)

NCCN



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

FAP/HNPCC

**Settled role for (procto)colectomy in FAP
Extended colectomy in HNPCC; TAH/BSO
Many positive NSAID trials in FAP, ASA in HNPCC**

NCCN



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

**The place for risk-reducing surgery clearly
established in BRCA, FAP, HNPCC, MEN...**

**Medical approaches-“chemoprevention” less
well settled, as trials very difficult**



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute



The Future of Cancer Prevention in Inherited Syndromes

None of the approaches, surgical or medical, have really gone to the heart of the underlying problem, pathogenic variants in various housekeeping genes

Addressing these calls for either modifying the DNA, RNA, or associated proteins

Or one form or another of genetic selection: egg or sperm donation, preimplantation diagnosis (PGD) or prenatal diagnosis. For any of these, prospective parents must be aware of diagnosis in the family and willing/able to pursue these options



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

BRCA Carriers

**Discuss option of risk-reducing mastectomy
RRSO at 35-40 after child-bearing complete
(40-45 in BRCA2)**

Tamoxifen lowers risk (with if's, and's, but's)

Possible role for aromatase inhibitors

PGD considered (w cautionary comments)

NCCN



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI


Comprehensive
Cancer Center

A Cancer Center Designated by the
National Cancer Institute

https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/

Embryo testing and treatme... X This page can't be displayed

File Edit View Favorites Tools Help

 Human Fertilisation & Embryology Authority

Home | Contact us

I am... | Treatments | Donation | Choose a clinic | About us

Embryo testing and treatments for disease

Embryo testing and treatments can be used by people who have serious inherited diseases in their family and want to avoid passing the disease onto their children. Find out what your options are and how to get started.

11:48 AM
4/12/2020



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

Browser address bar: <https://www.hfea.gov.uk/pgd-conditions/?condition=Hereditary+Nonpolyposis+Colorectal+C>

PGD conditions | Human Fe... | This page can't be displayed

File Edit View Favorites Tools Help

Human Fertilisation & Embryology Authority

I am... | Treatments | Donation | Choose a clinic | About us

Condition

Hereditary Nonpolyposis Colorectal Cancer: Lynch Syndrome (for all subtypes)

OMIM #

Status

All

Filter

Condition name	Status	OMIM number	Documents
Hereditary Nonpolyposis Colorectal Cancer: Lynch Syndrome (for all subtypes)	approved		

Windows taskbar: 11:54 AM 4/12/2020



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

Browser address bar: [https://www.hfea.gov.uk/pgd-conditions/?condition=BRCA+1+\(increased+susceptibility+to+breast+cancer\)](https://www.hfea.gov.uk/pgd-conditions/?condition=BRCA+1+(increased+susceptibility+to+breast+cancer))

PGD conditions | Human Fertilisation & Embryology Authority

This page can't be displayed

File Edit View Favorites Tools Help

Human Fertilisation & Embryology Authority

I am... | [Treatments](#) | [Donation](#) | [Choose a clinic](#) | [About us](#)

Condition

BRCA 1 (increased susceptibility to breast cancer)

OMIM #

Status

All

Filter

Also, MEN, Li-Fraumeni, others

Condition name	Status	OMIM number	Documents
BRCA 1 (increased susceptibility to breast cancer)	approved	113705	

Windows taskbar: 11:56 AM 4/12/2020

←


→

https://www.hfea.gov.uk/pgd-conditions/?condition=BRCA+1+(increased+susceptibility+to+breast+cancer)

PGD conditions | Human Fe...

This page can't be displayed

FileEditViewFavoritesToolsHelp

Human Fertilisation & Embryology Authority

I am... | Treatments | Donation | Choose a clinic | About us

Condition

BRCA 1 (increased susceptibility to breast cancer)

OMIM #


Status


All

Filter

Also, MEN, Li-Fraumeni, others

Condition name	Status	OMIM number	Documents
BRCA 1 (increased susceptibility to breast cancer)	approved	113705	





11:56 AM
4/12/2020

Issues in PGD/PND

Requires awareness of genetic dx

Costs of PGD

PGD success comparable to normal

In BRCA, concerns about hormone stimulation

Ethics of PND (late-onset disease w relatively effective interventions)

Conditions unlikely to be diagnosed in the absence of *universal* universal testing

CMMRD: Biallelic MMR (typically PMS2)

Biallelic MSH3

MYH polyposis (MAP)

Biallelic BRCA1/2 (Fanconi anemia)

Any case of adoption where parentage unknown

Any case of false paternity

Several of these associated with pediatric malignancies, with little or no FH

Does all this provide a rationale for consideration of truly universal testing—ie really test everybody for everything?

Recessive disorders—MYH, CMMRD commonly only preventable if parents of known mutation status, or if PND done on routine basis

Short of this, and for these and dominant disorders, neonatal or otherwise early testing worth considering



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center

NCI

Comprehensive
Cancer Center

A Cancer Center Designated by the
National Cancer Institute

The screenshot shows a web browser window displaying a Wired article. The browser's address bar shows the URL: <https://www.wired.com/story/why-does-covid-19-make-some-people-so-sick-ask-their-dna>. The Wired logo is prominently displayed at the top of the page, along with navigation links for 'DIY FACE MASK', 'GUIDE: ESSENTIALS', 'HOW TO DISINFECT EVERYTHING', 'SHELTER IN PLACE TRACKER', 'FAQS', 'NEWSLETTER', and 'LATEST NEWS'. The article is by Megan Molteni, dated 04.07.2020 at 01:27 PM, and is categorized under 'SCIENCE'. The main headline reads 'Why Does Covid-19 Make Some People So Sick? Ask Their DNA'. Below the headline, a sub-headline states: 'Consumer genomics company 23andMe wants to mine its database of millions of customers for clues to why the virus hits some people harder than others.' The article's featured image is a stylized graphic showing a grid of vertical bars, some of which are highlighted in yellow, representing genetic data. The browser's taskbar at the bottom shows various application icons, including the Windows Start button, File Explorer, and several open applications like Microsoft Edge, Outlook, and PowerPoint. The system clock in the bottom right corner indicates the time is 11:31 AM on 4/10/2020.

7

8

9

10

11

12

13

14

15



AT THE FOREFRONT

UChicago Medicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

What about COVID-19?

So, could genetics help explain why certain people develop severe COVID-19 and others develop only mild or undetectable symptoms?

It's too early to say for sure, but some scientists think that's likely the case. At least a couple of studies have started looking for clues.

For example, in order to get inside our cells, the virus that causes COVID-19 latches onto a human protein called ACE2. And scientists [identified](#) genetic variants in and near the ACE2 gene that could impact how much ACE2 protein is made, or how the protein functions. This could make it easier or tougher for the virus to slip inside a person's cells and make them sick. In another study, scientists [reported](#) that a person's blood type — which is determined by the *ABO* gene — might influence their likelihood of being infected by the virus. While these preliminary observations are intriguing, more research in different populations and in larger groups of patients is needed to validate these and other findings.

23 and me Website



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

What about COVID-19?

One way to identify genetic variants that contribute to disease severity is a genome-wide association study or GWAS.

In a GWAS, scientists compare the DNA of people who had severe symptoms to the DNA of people who had milder symptoms, or even no symptoms at all.

Genetic variants that are more common in one of these groups of participants than the other represent genetic associations with COVID-19 severity.

23 and me Website



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

Conclusion

So it immediately occurs to us to look at the spectrum of sick for clues as to genetic susceptibility to lethality of Covid-19

Once variable susceptibility established (if it is) we believe the stakes are high enough and cost low enough as to consider testing the entire population for such susceptibility

Under the circumstances, would it not make sense to think about genetic risk of cancer in the same universal terms?