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Personal Perspectives on Henry Lynch and Future Directions in Preventive Oncology

Patrick Lynch, JD, MD
Professor of Medicine
UT MDACC

19 April 2020

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Disclosures

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

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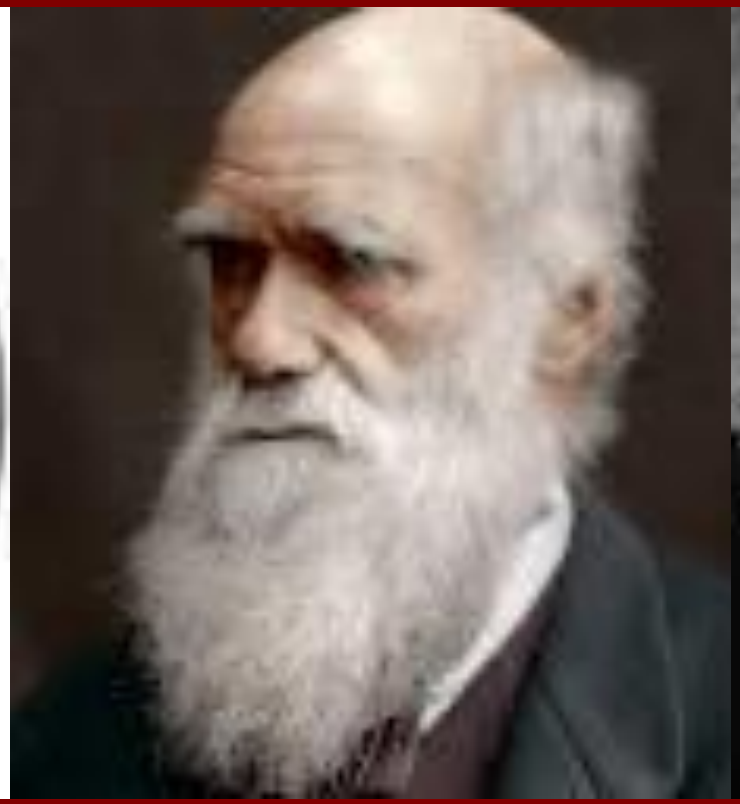


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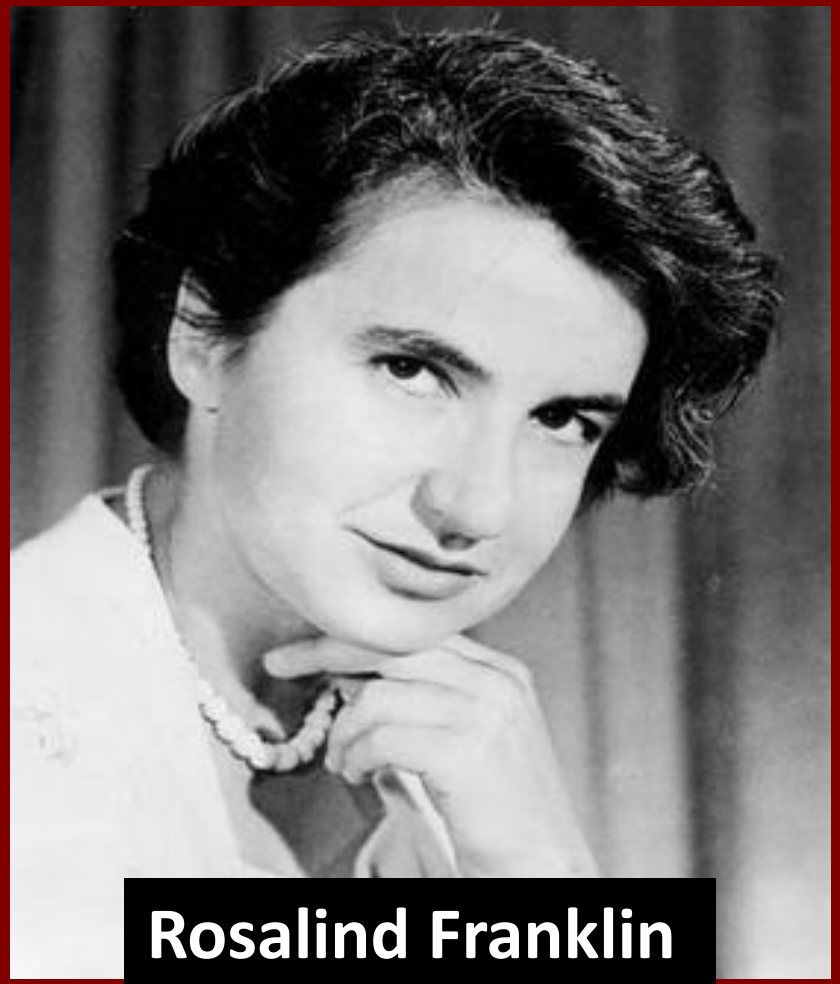
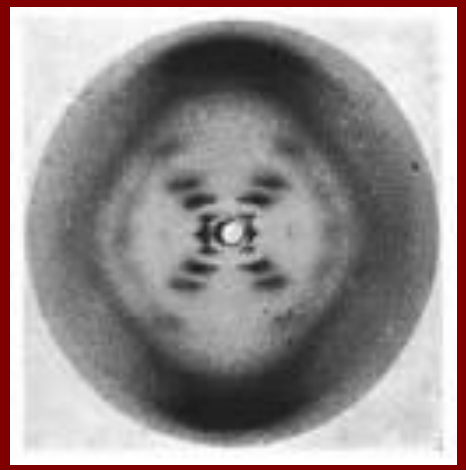


Rosalind Franklin
1920-1958



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

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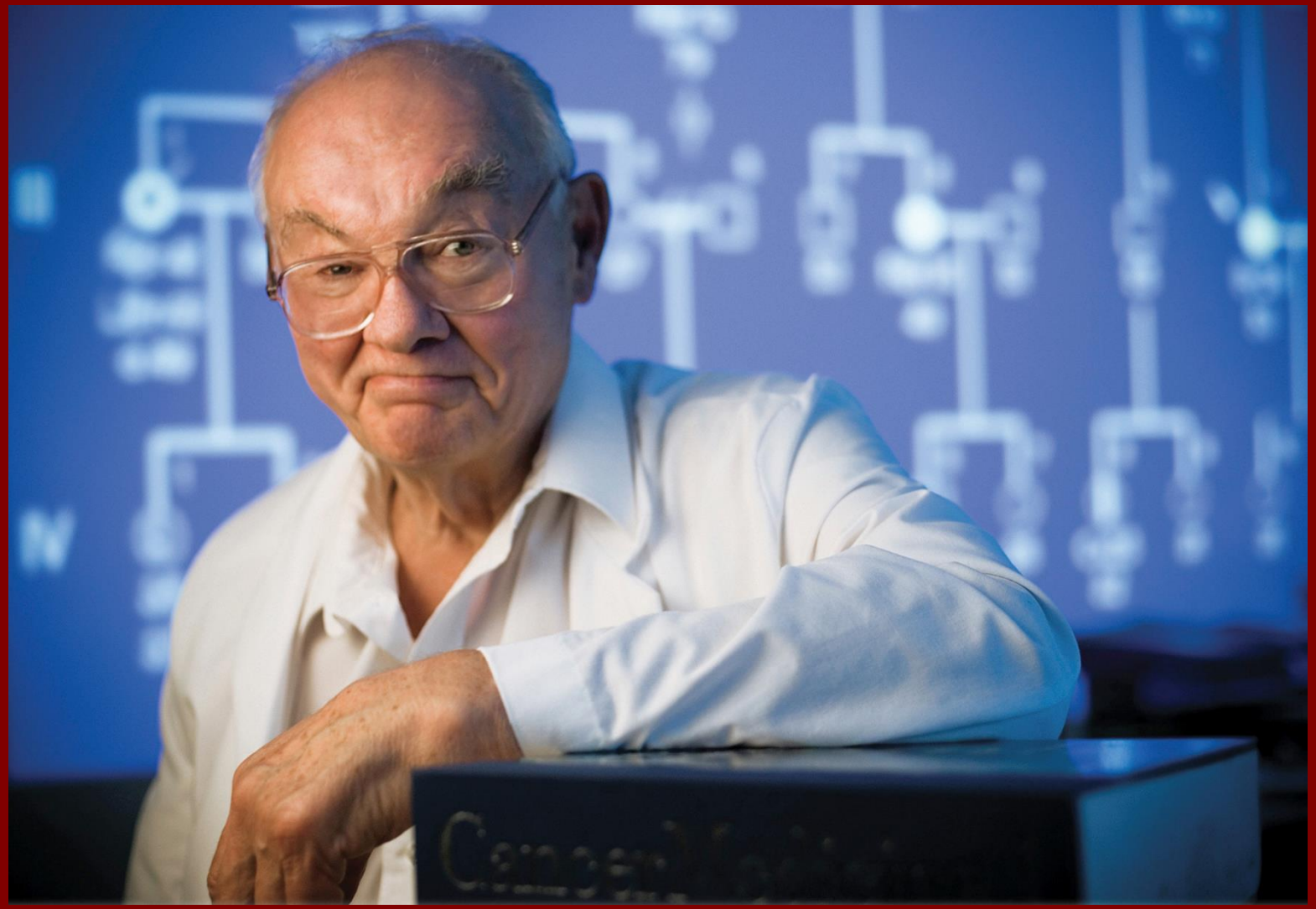

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Mass>>NY>US navy>west>>>Tx>>>>>Neb

1928 30’s ’44-45 40’s-50 ‘50-’60 60’s-2019

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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.

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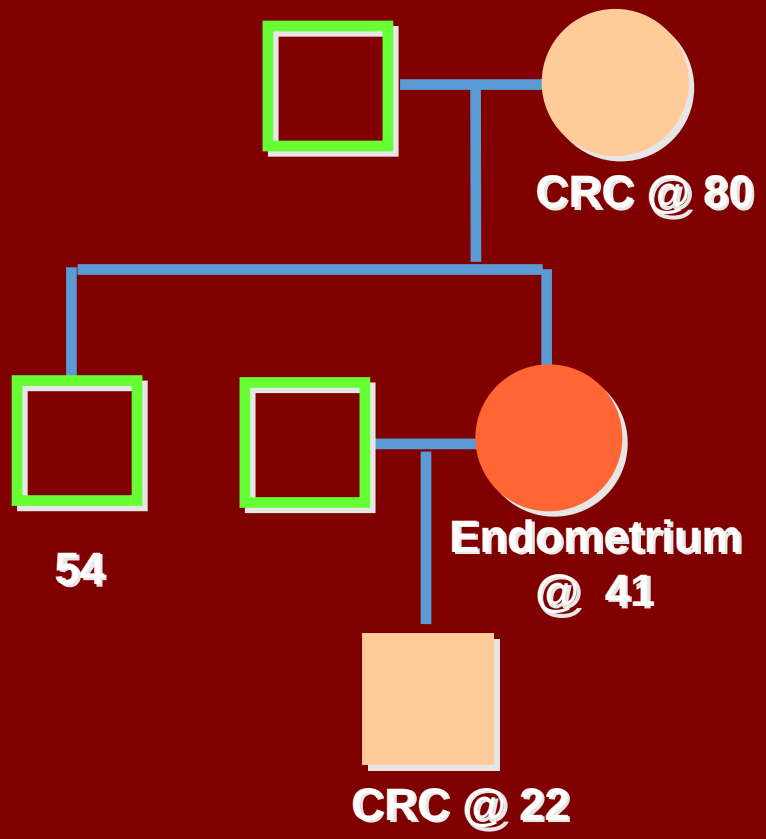

Amsterdam Criteria II

- 3 or more CRC (*or HNPCC-associated tumors*)
- 2 or more generations
- 1 affected age by 50, 1 case a 1^0 relative of the other two
- Attenuated FAP excluded

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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

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Cancer Prevention In Genetic Syndromes

"I'll have an ounce of prevention."

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

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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)

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FAP/HNPCC

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

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

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

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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

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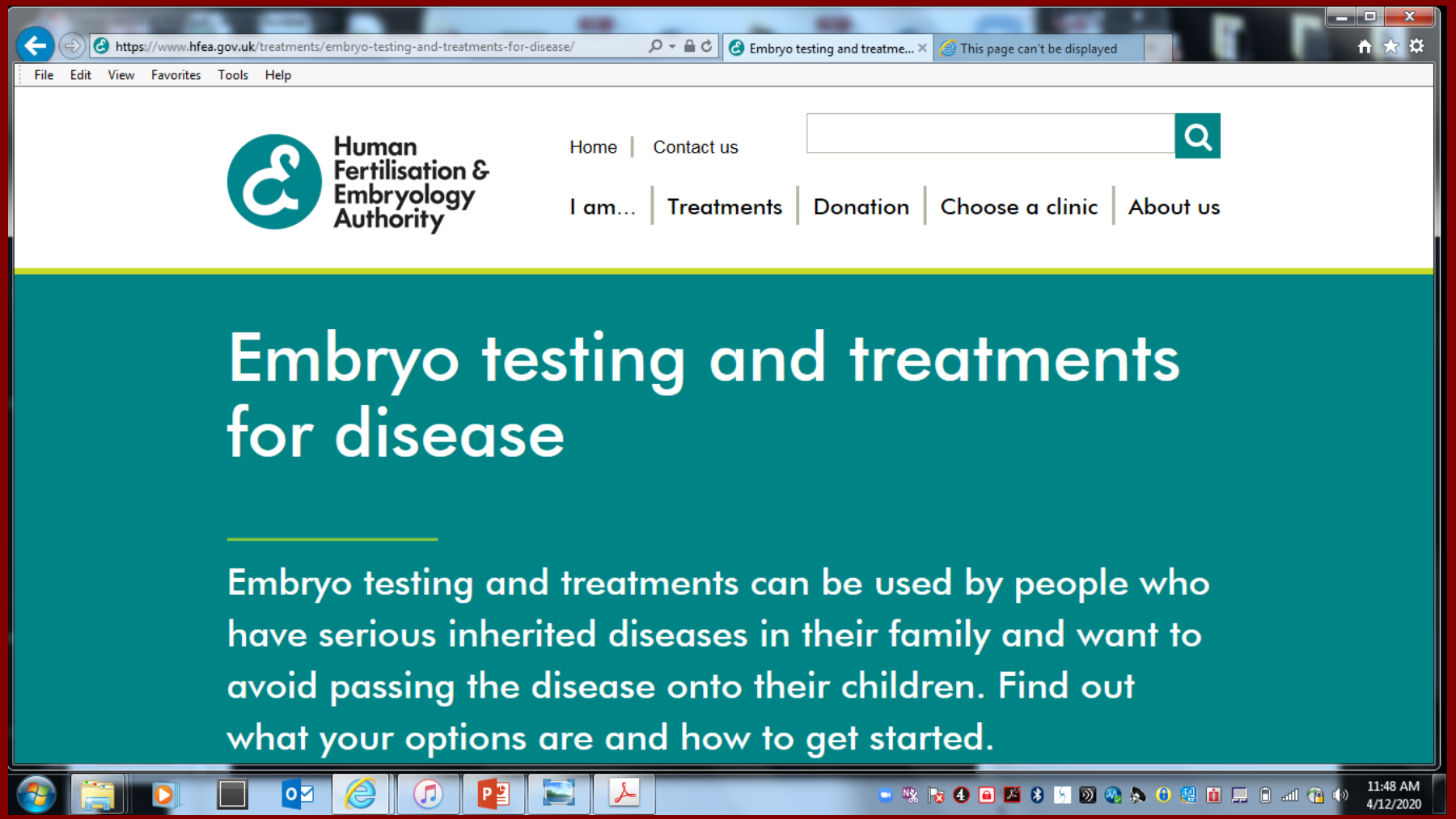

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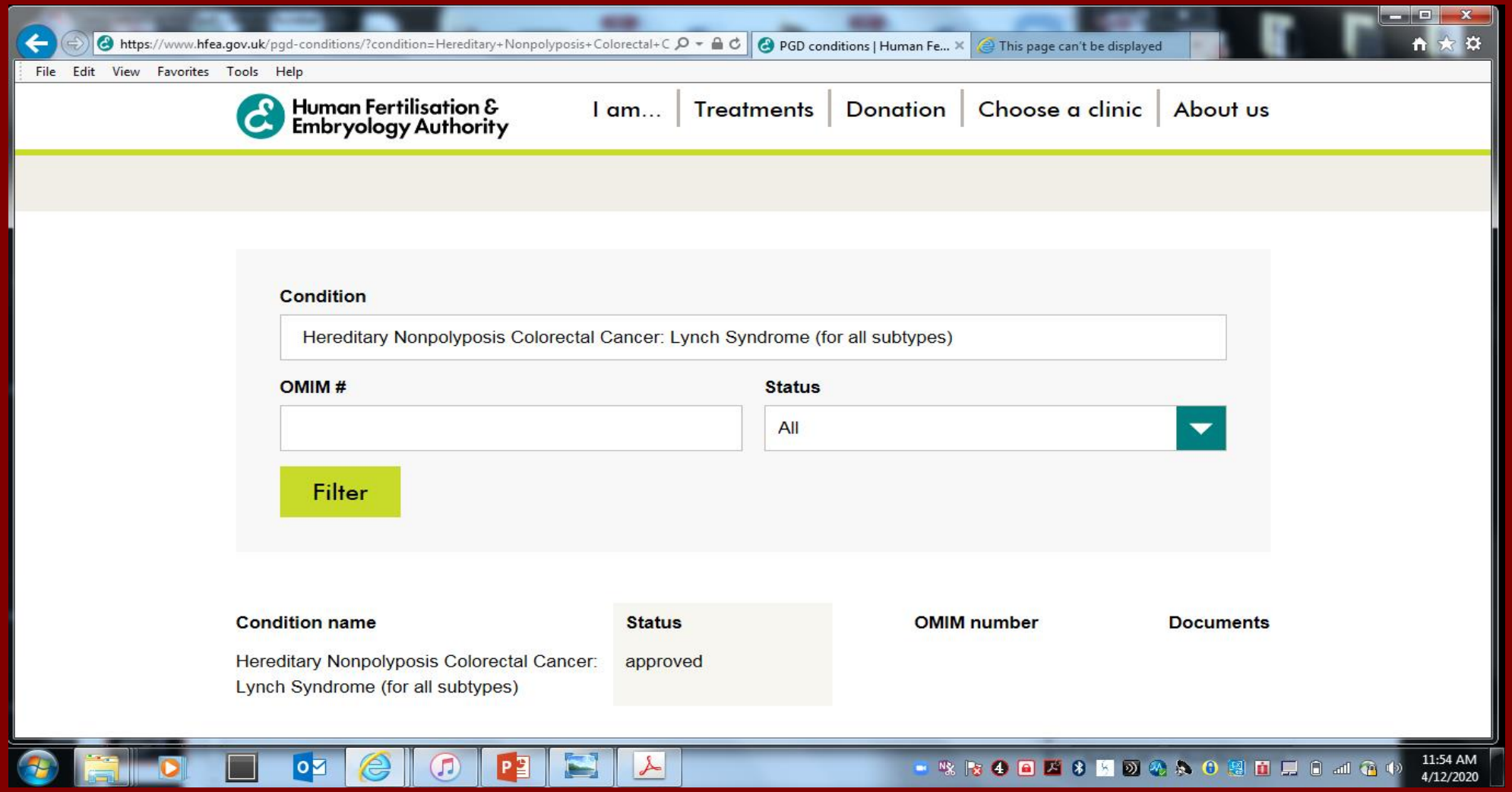

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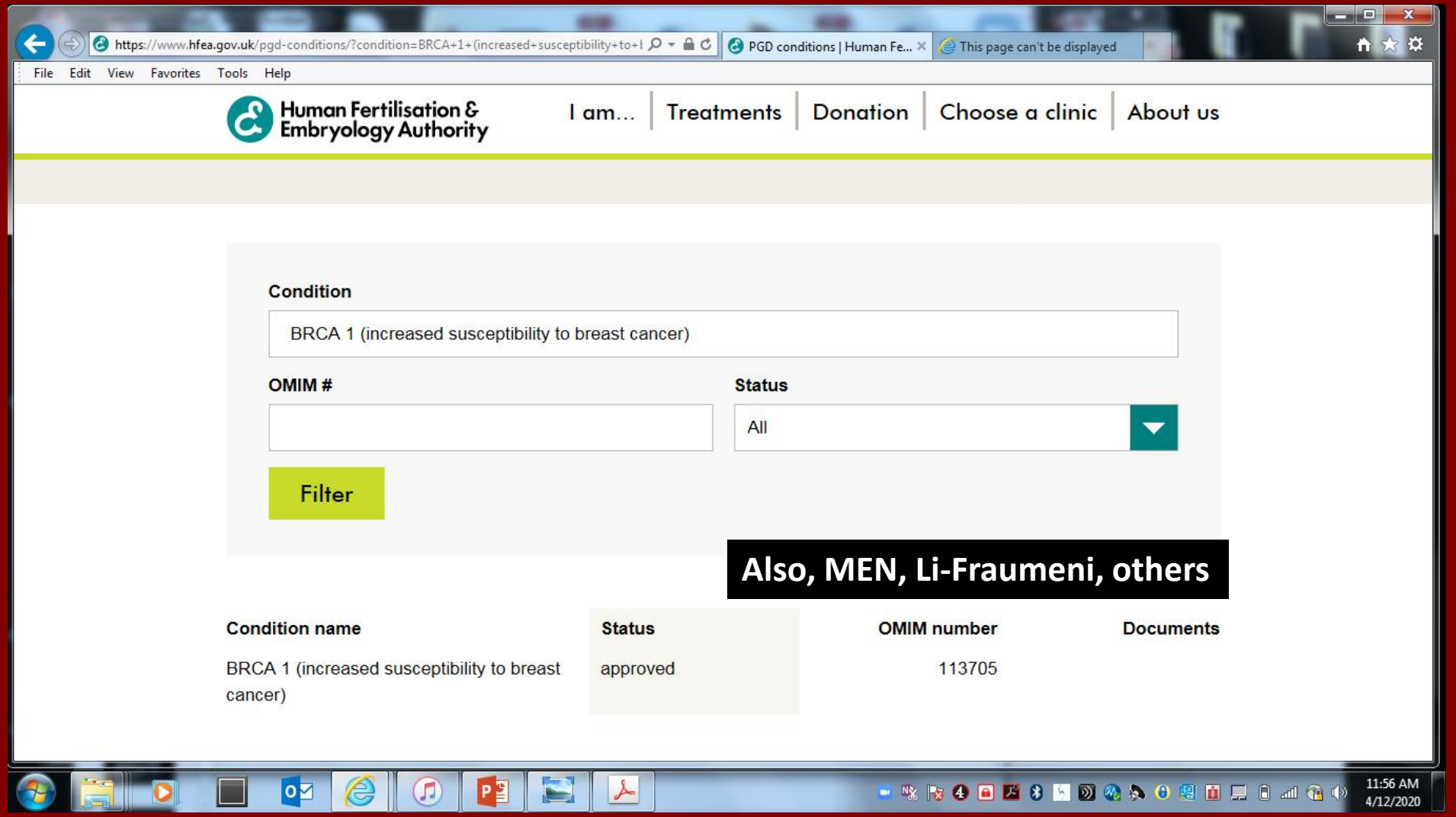

https://www.hfea.gov.uk/pgd-conditions/?condition=BRCA+1+(increased+susceptibility+to+l

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

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

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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

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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

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?