



AT THE FOREFRONT

UChicagoMedicine

Comprehensive Cancer Center



A Cancer Center Designated by the
National Cancer Institute

Genetics 101

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Disclosures

- Co-Founder: CancerIQ
- Consultant or Advisory role: Tempus
- Research Collaboration: Myriad, Color, Novartis, Roche, Abbvie
- Advocacy Board: Susan G Komen, V Foundation



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Genetics in Oncology Care



Janet D Rowley, MD
1925-2013



Harvey M. Golomb, MD
Section Chief and Program Director
Former President ASCO



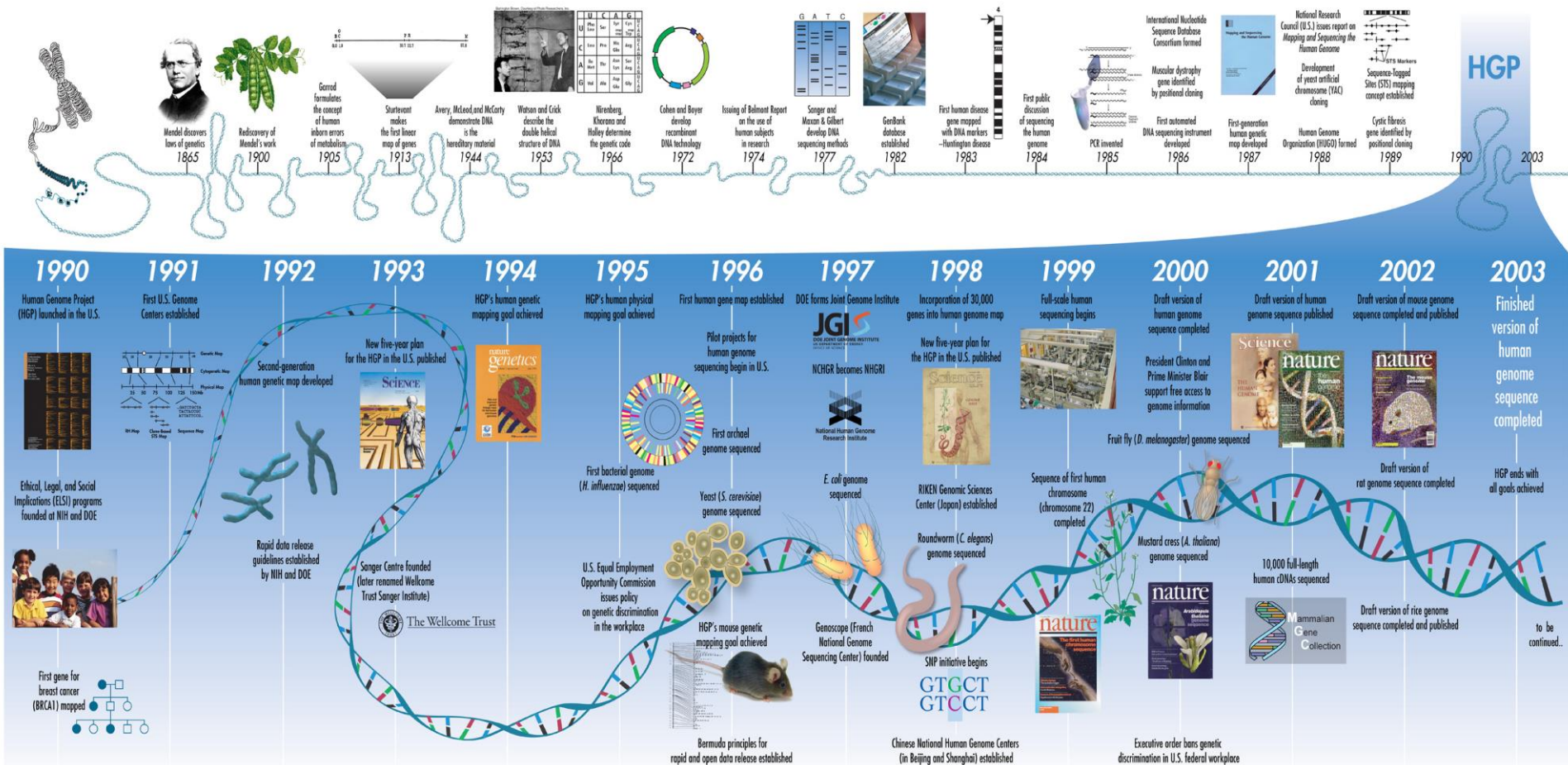
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Timeline of Genetic Discoveries



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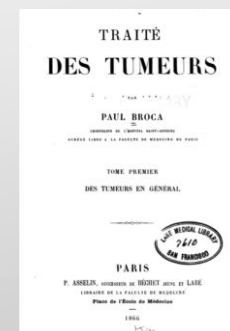
NCI Comprehensive Cancer Center

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Evidence for Heritability of Cancer

1866

Broca observed heritability based on wife's familial breast cancer



Interim

Twin/Family/Sibling studies...

1969

Li-Fraumeni observed familial clustering (*TP53*)



1971

Knudson postulated “two-hit” hypothesis for retinoblastoma



1991

Mapping of a familial breast cancer gene (*BRCA1*)



Cancer as a Genetic Disease

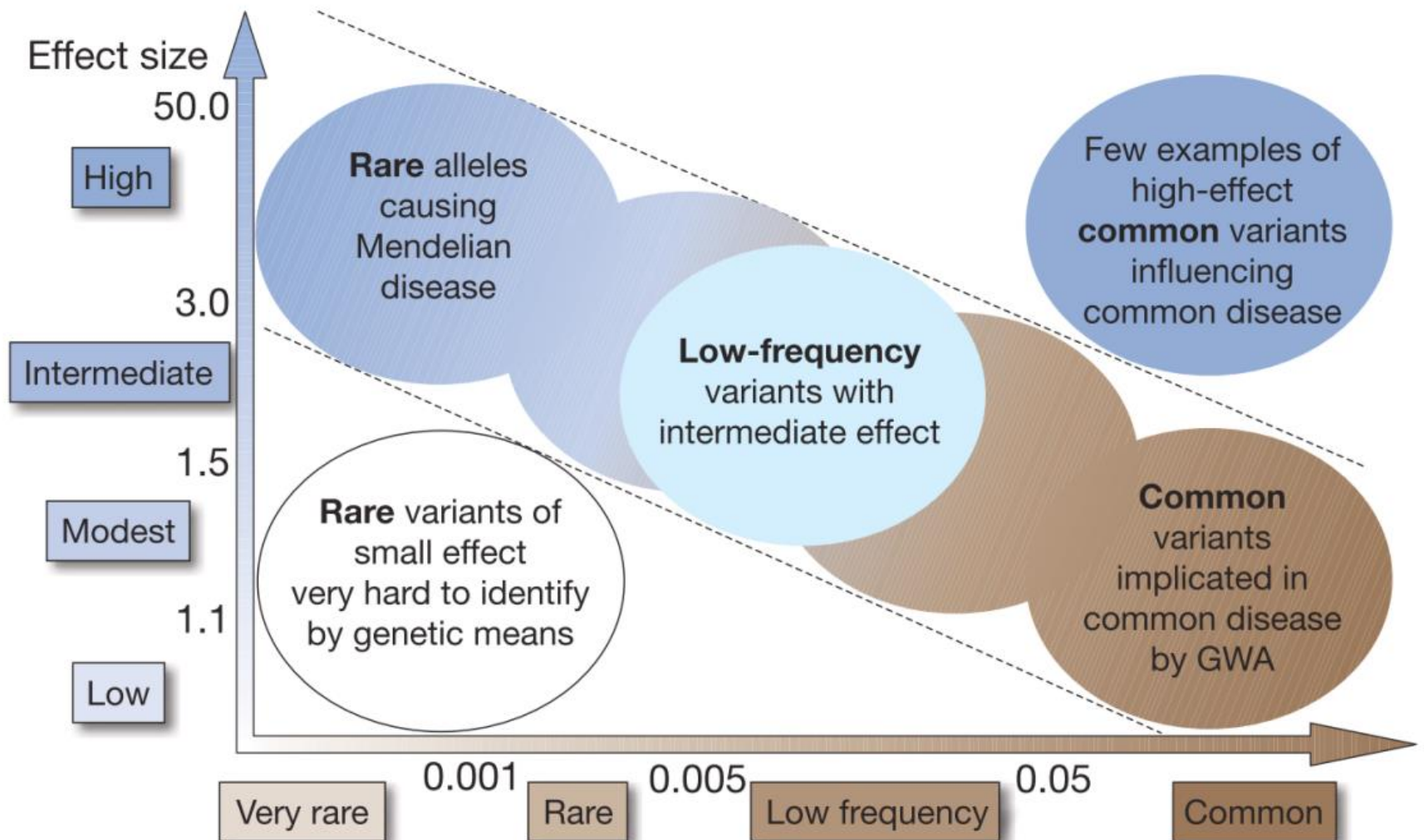
- 1866: BROCA's first significant description of a familial breast cancer family published in France
- 1913: first pedigree of a Lynch syndrome family published (colon cancer family study began in 1895)
- 1969: Li and Fraumeni describe breast cancer families with soft-tissue sarcomas, leukemia and lymphoma
- 1972: Rowley identified "Philadelphia" chromosome translocation as cause of leukemia. Risk adapted therapies for leukemia

Late 20th century brought about increased focus on identifying genetics underlying hereditary cancer

- 1987: Bodmer localized APC to chromosome 5
- 1990: MC King localized BRCA1 to chromosome 17q
- 1993: MSH2 discovered
- 1997: ASCO Cancer Genetics Education Task Force - 20th Anniversary
- 2017: Targeted therapies for inherited cancers become mainstream

Lynch H, et al. Am J Med Genet C Semin Med Genet, 2004.

Genetic Association Studies

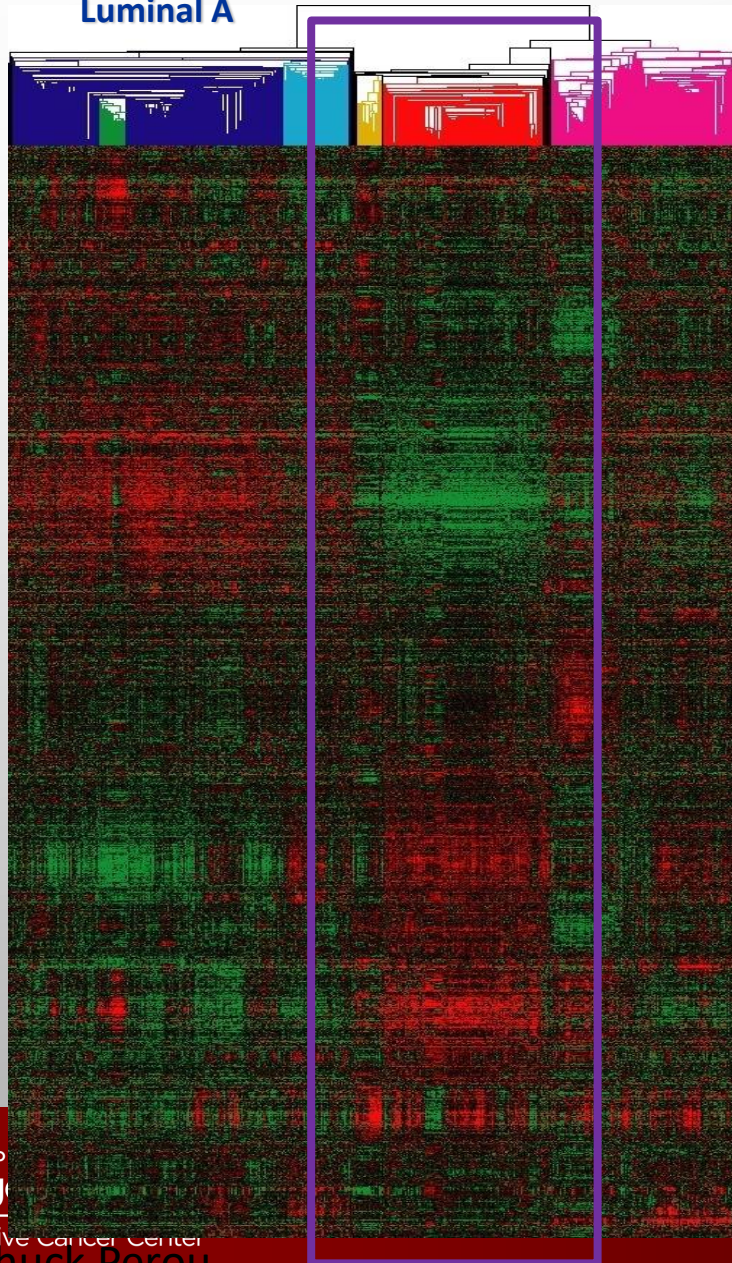


Lobular/Normal-like Claudin-low HER2-enriched

Luminal B

Basal-like

Luminal A



Estimated Cancer Deaths per year in the USA

Women
270,290



26% Lung & bronchus

10% Breast Luminal

9% Colon & rectum

7% Pancreas

5% Ovary

**5% TNBC
(ER-, PR-, HER2-)**

4% Non-Hodgkin
lymphoma

3% Leukemia

3% Uterine corpus

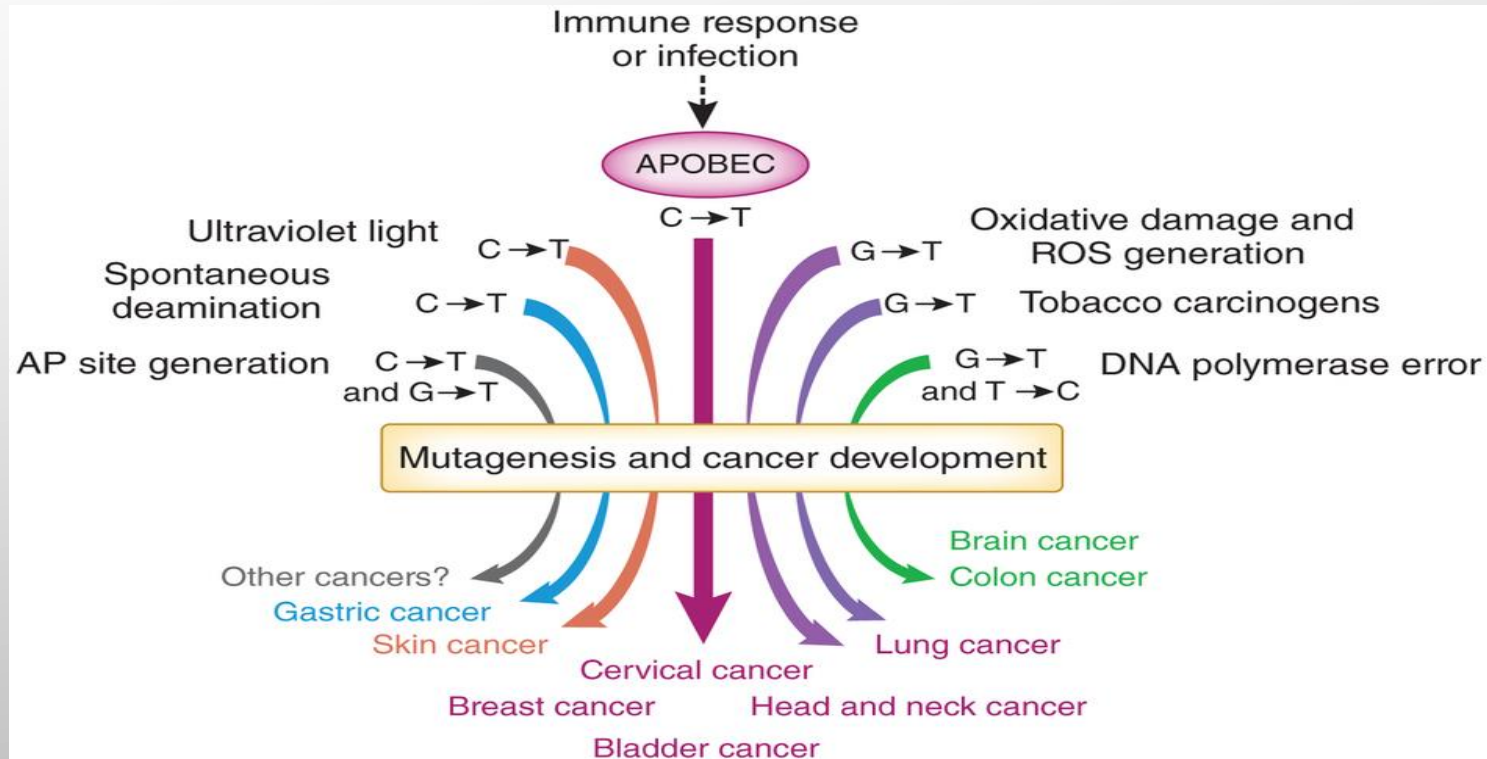
2% Liver & intrahepatic
bile duct

2% Brain/Other nervous
system

24% All other sites

Sources of Mutations

Known biological mechanisms



<http://www.nature.com/ng/journal/v45/n9/images/ng.2736-F1.jpg>

APOBEC is a family of cytidine deaminases involved in innate immunity
- Cause C>T or C>G substitutions at the TCW motif

Original Article

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

Hope S. Rugo, M.D., **Olufunmilayo I. Olopade, M.D.**, Angela DeMichele, M.D., Christina Yau, Ph.D., Laura J. van 't Veer, Ph.D., Meredith B. Buxton, Ph.D., Michael Hogarth, M.D., Nola M. Hylton, Ph.D., Melissa Paoloni, D.V.M., Jane Perlmutter, Ph.D., W. Fraser Symmans, M.D., Douglas Yee, M.D., A. Jo Chien, M.D., Anne M. Wallace, M.D., Henry G. Kaplan, M.D., Judy C. Boughey, M.D., Tufia C. Haddad, M.D., Kathy S. Albain, M.D., Minetta C. Liu, M.D., Claudine Isaacs, M.D., Qamar J. Khan, M.D., Julie E. Lang, M.D., Rebecca K. Viscusi, M.D., Lajos Pusztai, M.D., D.Phil., Stacy L. Moulder, M.D., Stephen Y. Chui, M.D., Kathleen A. Kemmer, M.D., Anthony D. Elias, M.D., Kirsten K. Edmiston, M.D., David M. Euhus, M.D., Barbara B. Haley, M.D., Rita Nanda, M.D., Donald W. Northfelt, M.D., Debasish Tripathy, M.D., William C. Wood, M.D., Cheryl Ewing, M.D., Richard Schwab, M.D., Julia Lyandres, B.S., Sarah E. Davis, M.S., Gillian L. Hirst, Ph.D., Ashish Sanil, Ph.D., Donald A. Berry, Ph.D., Laura J. Esserman, M.D., for the **I-SPY 2 Investigators**

N Engl J Med
Volume 375(1):23-34
July 7, 2016



Breakthrough Status for PARPi in Metastatic Prostate Cancer

January 2016

FDA Grants Olaparib Breakthrough Designation in mCRPC

Gina Columbus [@ginacolumbusonc](#)
Published: Thursday, Jan 28, 2016



Olaparib (Lynparza) has received an FDA breakthrough therapy designation as a treatment for patients with *BRCA1/2* or *ATM*-mutated metastatic castration-resistant prostate cancer (mCRPC) in those who have received a prior taxane-based chemotherapy and at least either hormonal agent.

October 2018

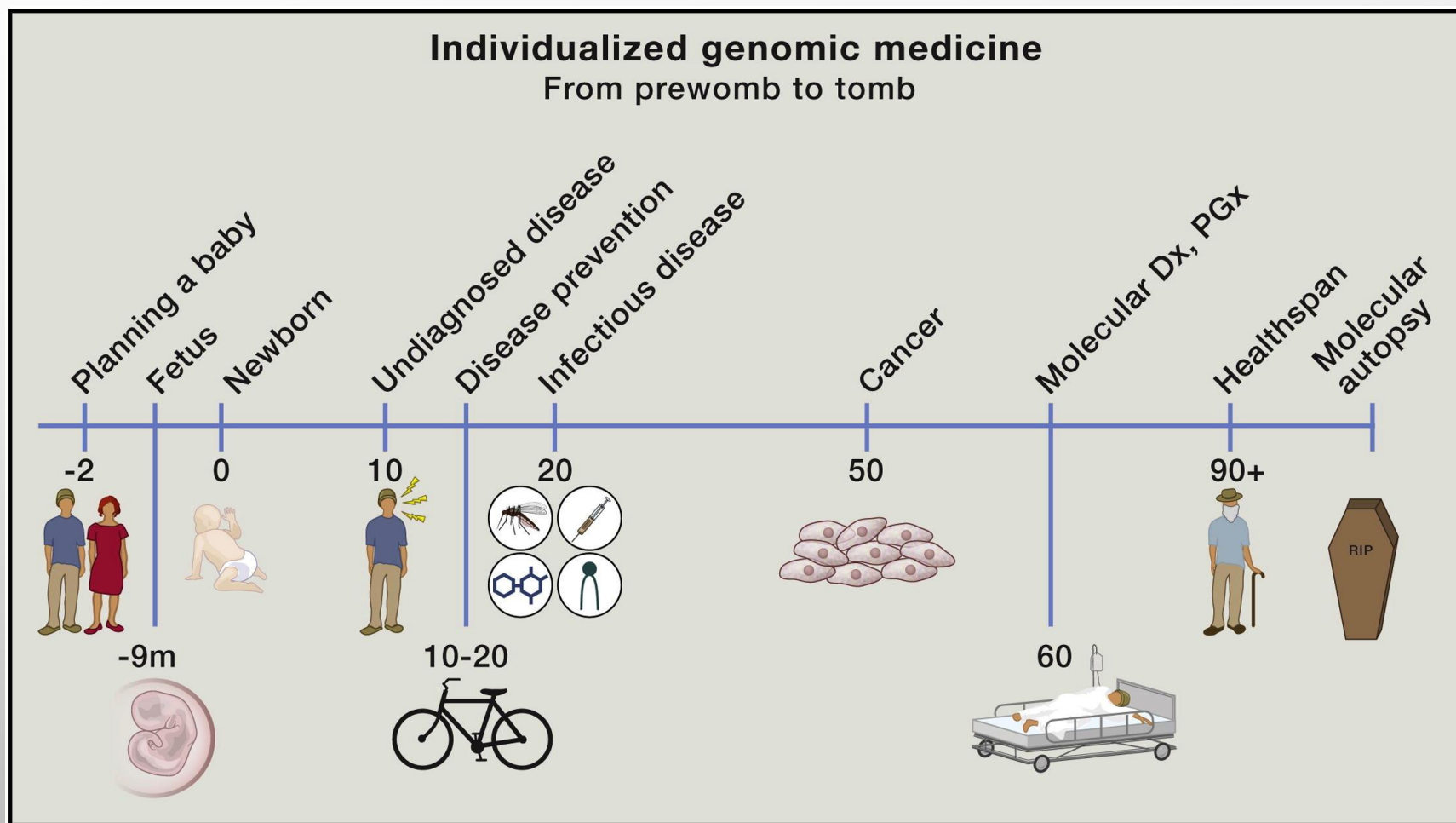
FDA Grants Rucaparib Breakthrough Designation for mCRPC

Ariela Katz
Published: Tuesday, Oct 02, 2018



The FDA has granted the PARP inhibitor rucaparib (Rubraca) a breakthrough therapy designation for single-agent use in adult patients with *BRCA1/2*-positive metastatic castration-resistant

Timeline of DNA Sequencing Applications in Medicine



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Cell. 2014 Mar 27;157(1):241-53.



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