Precision Medicine

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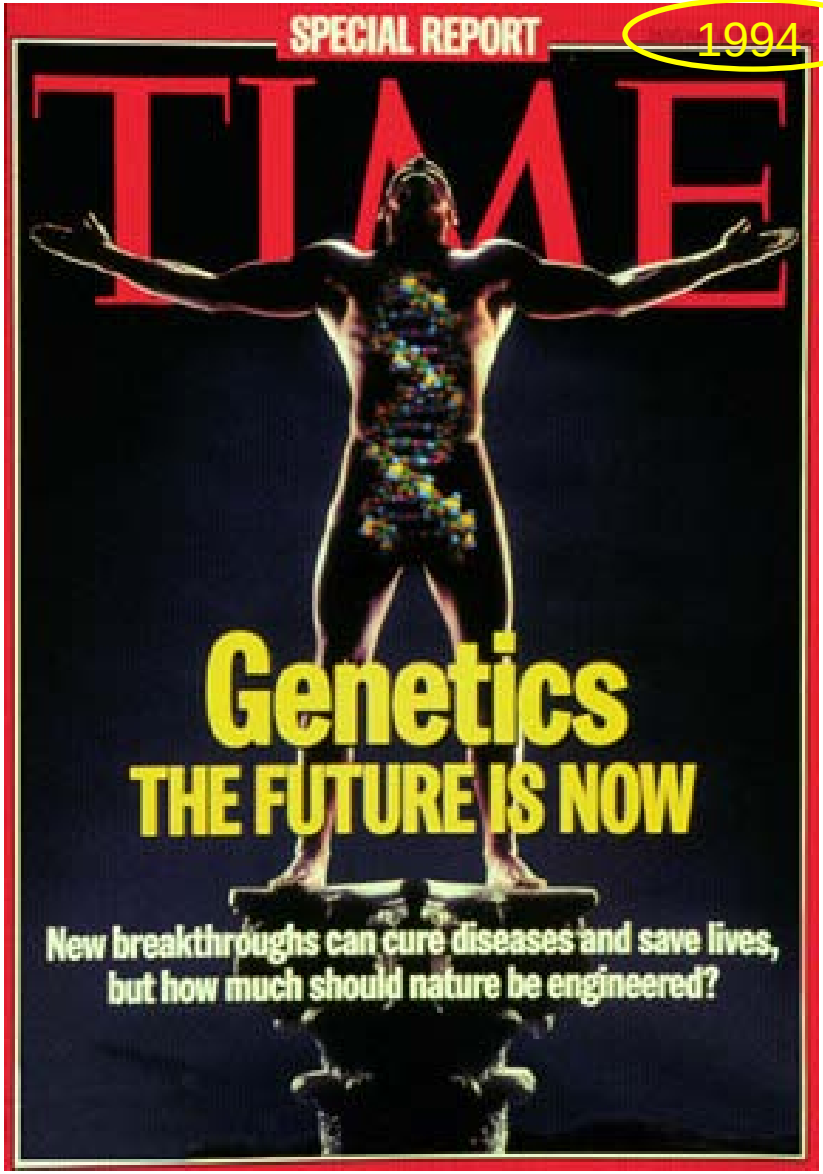
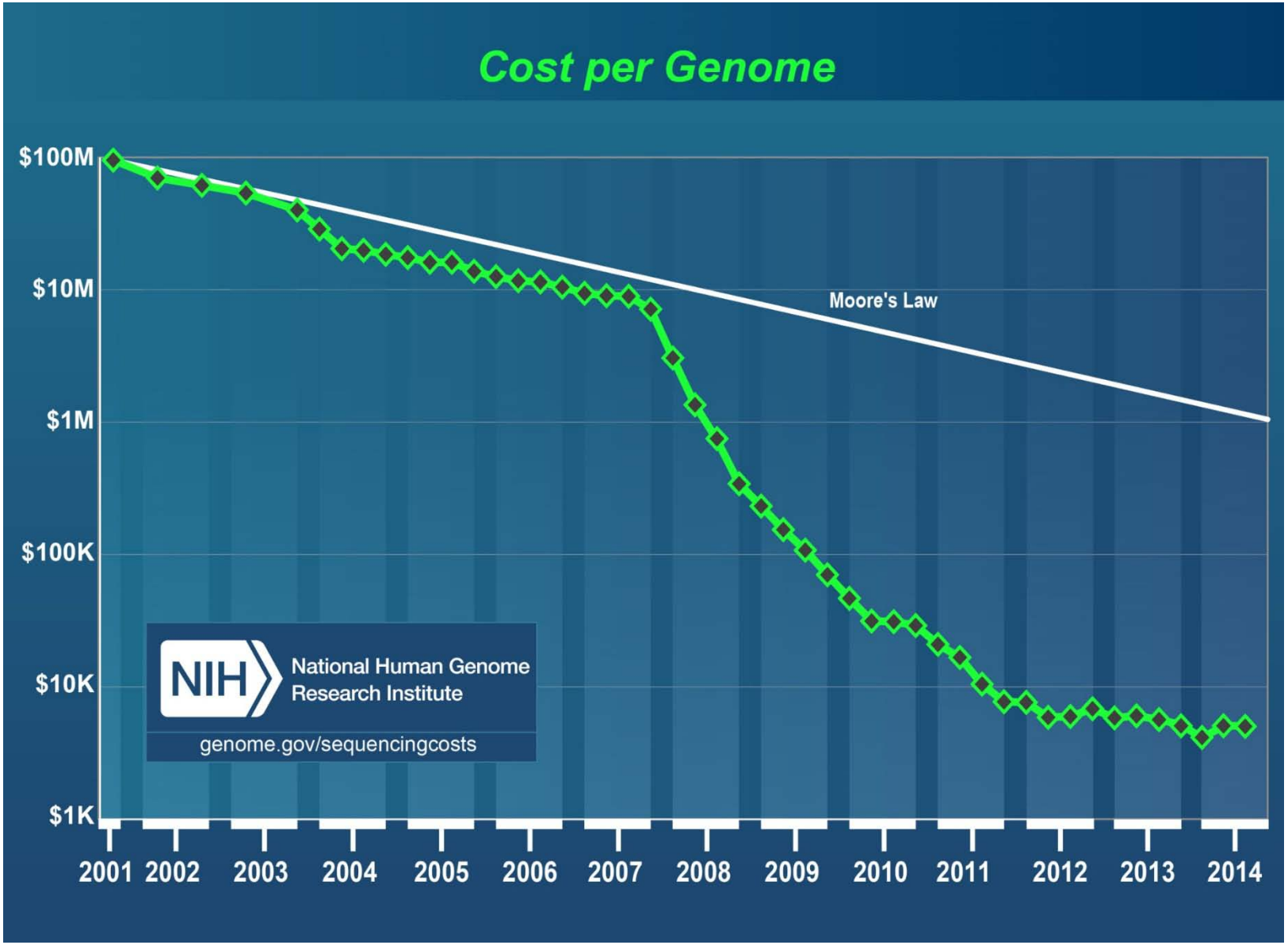
What is precision medicine?

- Providing the right treatment for the right patient at the right time and engaging the patient in a way that will enable them to maintain and improve their health and the health of their family.


SPECIAL REPORT
1994
TIME
Genetics
THE FUTURE IS NOW
New breakthroughs can cure diseases and save lives,
but how much should nature be engineered?

The Cost of Sequencing Has Declined



Seizures

- 9 year old female
- Seizures and dyskinesia at birth, microcephaly, intellectual disability
- No known family history of similar symptoms

Positive for a mutation in SLC2A1 Causing GLUT1 deficiency syndrome

- GLUT1 deficiency syndrome is due to the inability to transport glucose to the brain
- Diagnostic Implications:

  In individuals with SLC2A1 mutations, a ketogenic diet often improves seizure control and reduces paroxysmal events, although cognitive impairment persists.

  Mutation-specific testing for the SLC2A1 mutation showed this was a de novo mutation.

Complexities of Genetic Diagnostics

- Analysis of a genome identifies thousands of genetic variants, many of which have never been observed before.
- The methods used in the lab to generate data and interpret the data are highly complex and still evolving. Changes are made on a quarterly basis and result in significant improvements.
- Limiting patient access to these innovations jeopardizes patients' health.

• Why a diagnosis matters

•Ends the diagnostic odyssey which may involve invasive/expensive tests
•Prognosis, ability to tailor health maintenance
•Identifies treatment options
•Risk of recurrence, ability to prevent having other affected children if desired
•Closure about how this happened

- Cost Analysis Before WES
- (without including cost of the hospitalization)

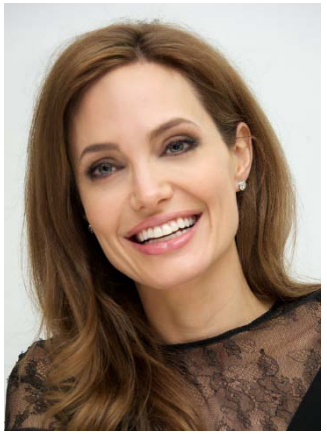
Imaging Cost	$5,979
Laboratory Tests Cost	$1,221
Other Testing (including biopsy)	$887
Genetic testing /Karyotype/ Chromosome microarray	$14,425
Total Cost	**$22,512**

Opportunities in Precision Medicine

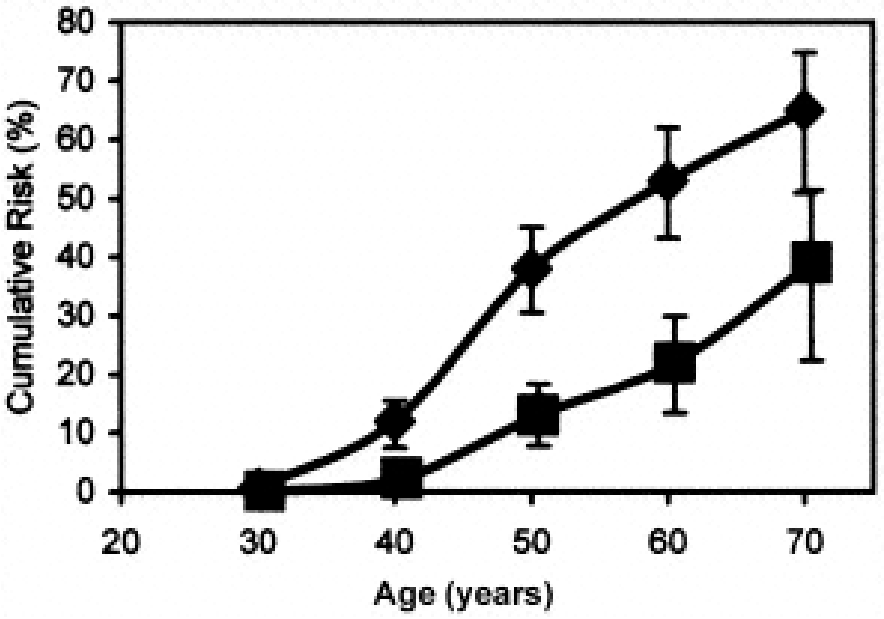
	2004	2014
Cost of sequencing a human genome	$22,000,000	$1000 to $5000
Time to sequence a human genome	2 years	<1 day
Number of smart phones in the United States	1 million (<2% of population)	160 million (58%)
Health providers using electronic records	20 % to 30%	>90%
Computer power	n	n x 16

Jocelyn Kaiser Science 2015;347:817

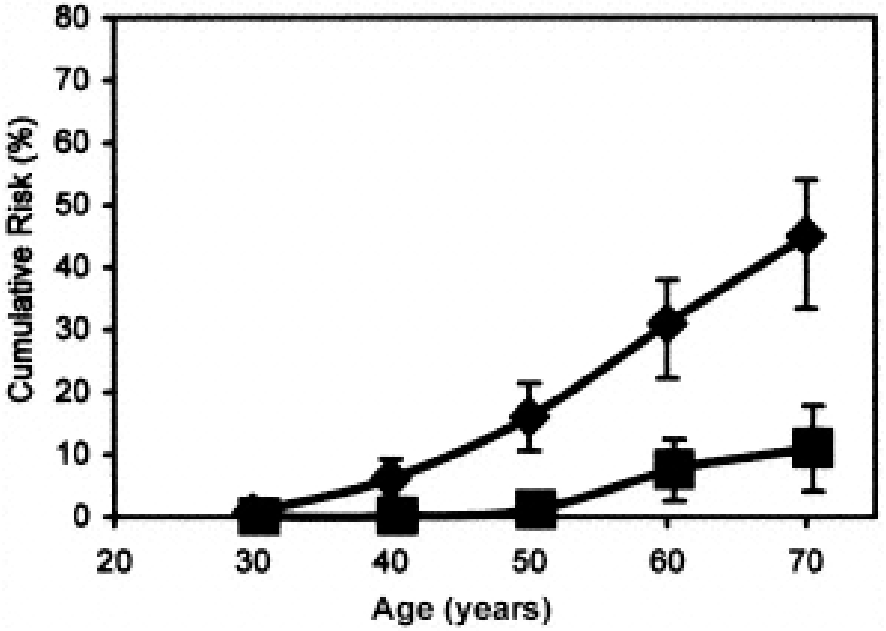
Cumulative Risk of Breast and Ovarian Cancer



BRCA1



BRCA2



Clinically Available Molecular Diagnostics along the continuum from health to disease in cancer and cardiovascular disease

	Cancer		Cardiovascular disease	
Time point in clinical decision making	**Test**	**Indication**	**Test**	**Indication**
Risk/susceptibility	*BRCA1, BRCA2* *HNPCC, MLH1, MSH2,* *TP53, PTEN*	Breast Colon Sarcomas	*KIF6, 9p21* *LQT gene panels*	CAD LQTS
Screening	HPV genotypes	Cervical	Corus CAD	CAD
Diagnosis	Lymphochip	Lymphoma	Corus CAD	CAD
Prognosis	Oncotype DX (21-gene assay) MammaPrint (70-gene assay) Her2/neu, ER, PR	Breast	Tnl, BNP, CRP	ACS
Pharmacogenomics	Her2/neu *UGT1A1* *KRAS* *EGFR* Amplichip; DMET *CYP2D6/CYP2C19*	Herceptin IrinotecanCetuximabEriotinib, Gefitinib Various others	*KIF6, SLCO1B1,* Amplichip; DMET *CYP2D6/CYP2C19* *VKORC1*	Statins Warfarin Various others
Monitoring	CTCs	Tumor recurrence or progression	AlloMap gene profile	Transplant rejection

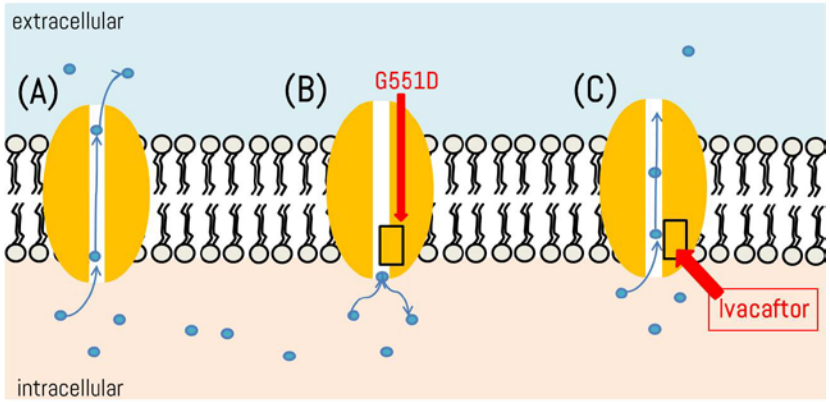
Annu. Rev. Genomics Hum, Genet. 2011 12:217-44

What's next?

- Mutation specific therapy
  - Cystic fibrosis: Ivacaftor/Kalydeco for G551D mutation (1200 patients at cost of $311,000/year)
  - Spinal muscular atrophy
- Gene editing
- Demonstrating cost effectiveness
- Predictive testing
  - Will need real time measurement of disease progression with biomarkers

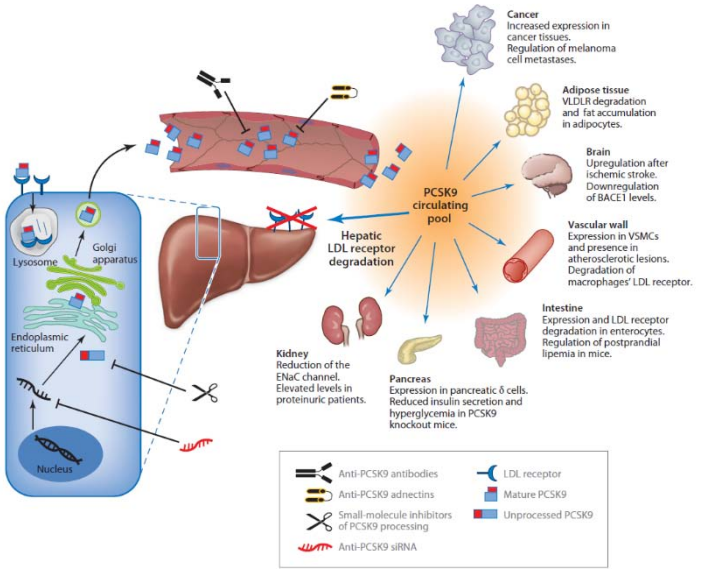
Ivacaftor (Kalydeco) for treatment of cystic fibrosis

- Drug for patients with one mutation- G551D (affects 4% of all ~70,000 cases of CF)
- Identified in small molecule screen as VX-770
- Mechanism of action: binds and opens CFTR channel protein
- Outcomes
  - Improvement of lung function
  - Changes in CF respiratory symptoms
- Cost of drug: $311,000 per year

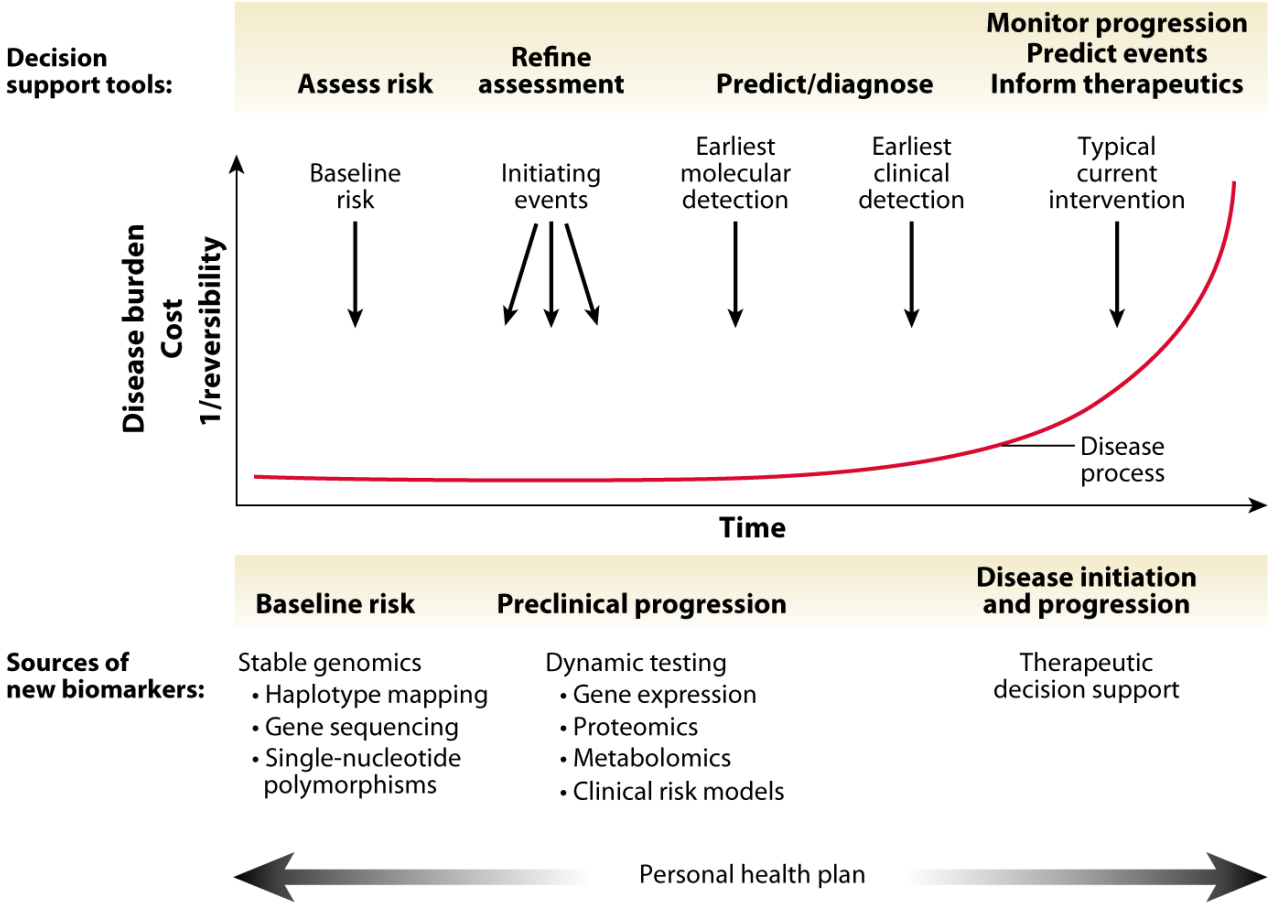


Proprotein convertase subtilisin/kexin type 9 (PCSK9)

- Involved in high cholesterol
- Genetically identified in individuals with high and low cholesterol
- Drugs that block PCSK9 lower LDL cholesterol to prevent hyperlipidemia
  - Monoclonal antibodies decreases bad cholesterol



Precision Medicine Through Life



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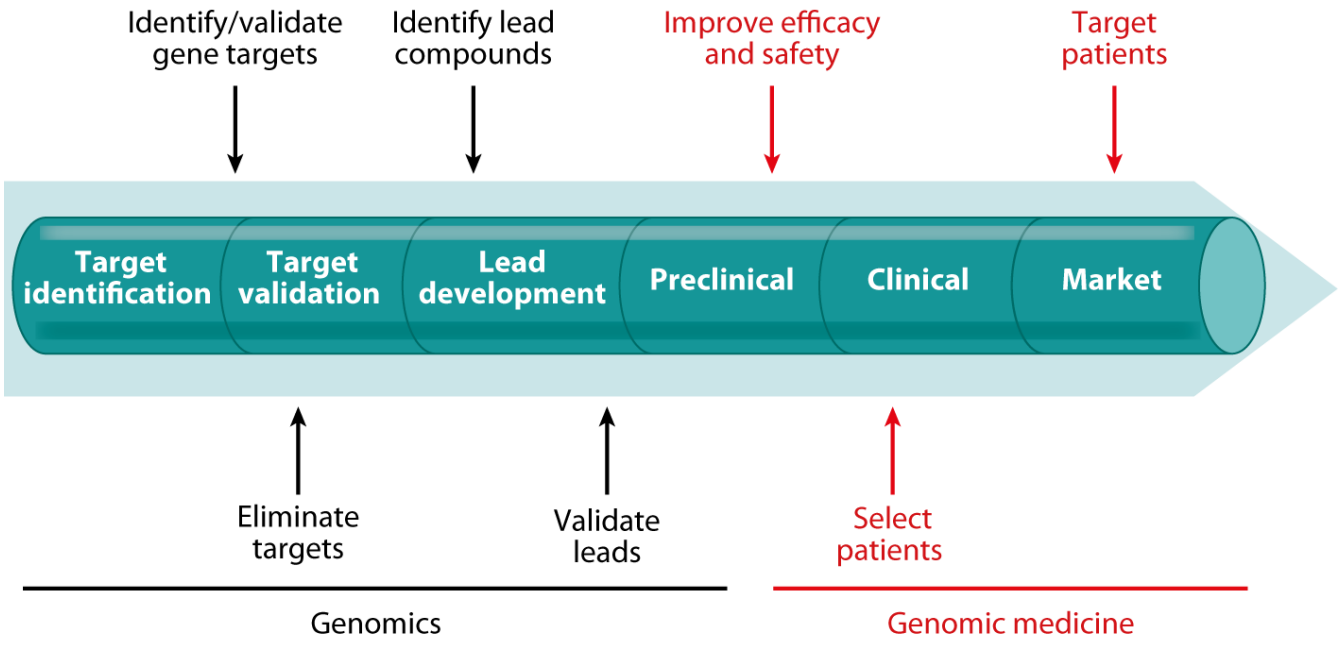
How Genomic Medicine Is Used in the Pipeline to Develop New Treatments



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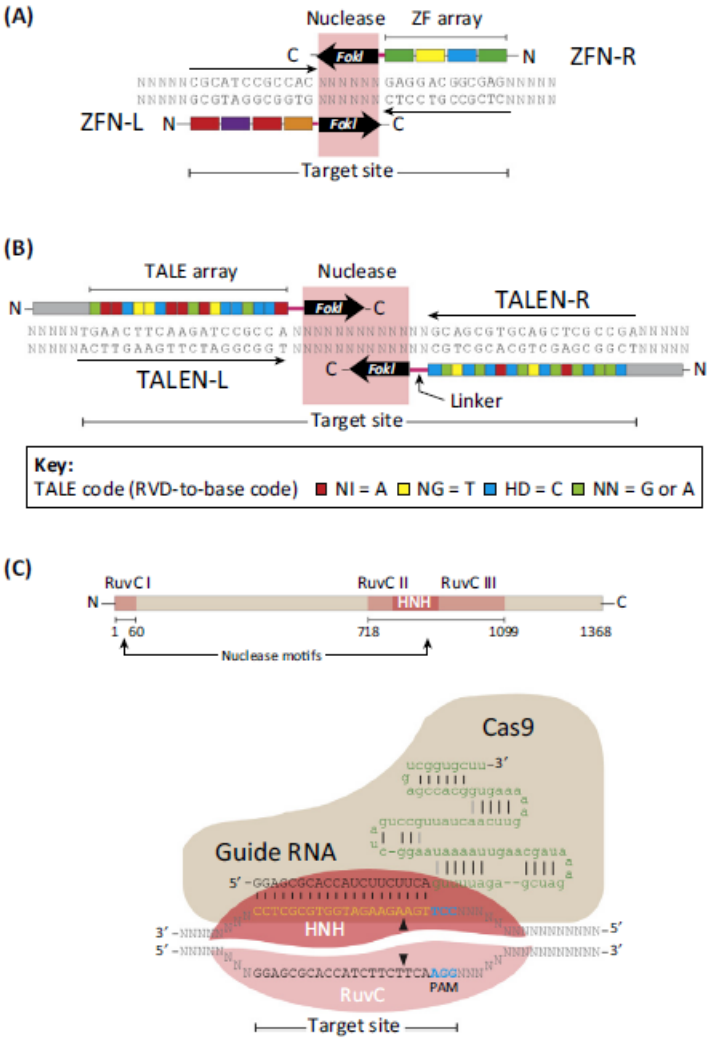
Gene editing as a treatment for genetic diseases

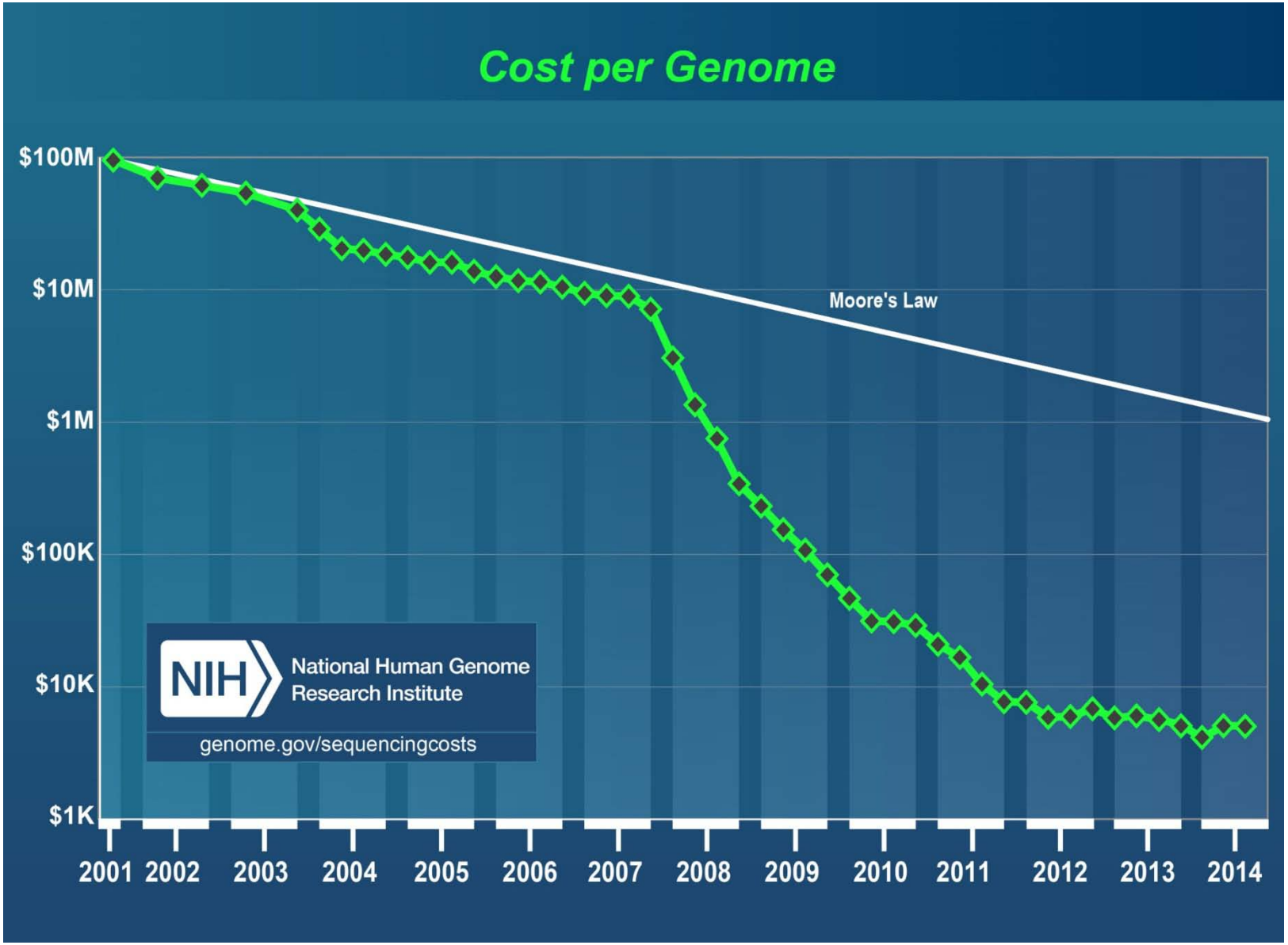
- DNA is inserted, replaced, or removed from a genome by programmable nucleases
- Targeted therapies aimed at disease mechanisms based on knowledge of genetic basis of disease



Challenges Ahead

- Interpretation of variants is challenging
  - Minority populations must be better represented
- Need to share data yet protect privacy
- Cost of sequencing is still high because of monopolies in the market

The Cost of Sequencing Is Not Declining



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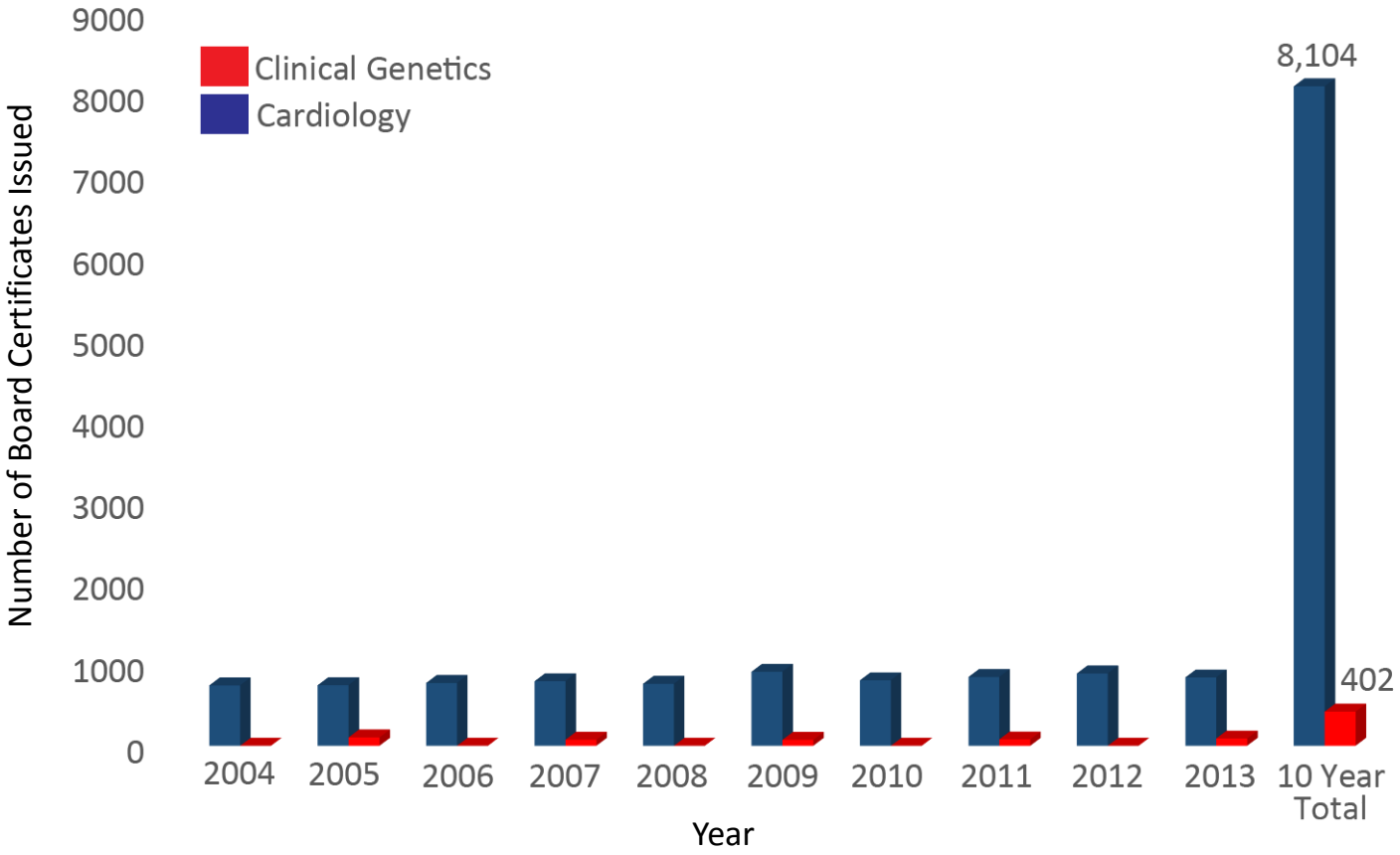
- Low genomic literacy of the public
- Insufficient genomic work force to deliver patient care

Insufficient Number of Medical Geneticists



American Board of Medical Specialties Board Certification Report 2013-2014

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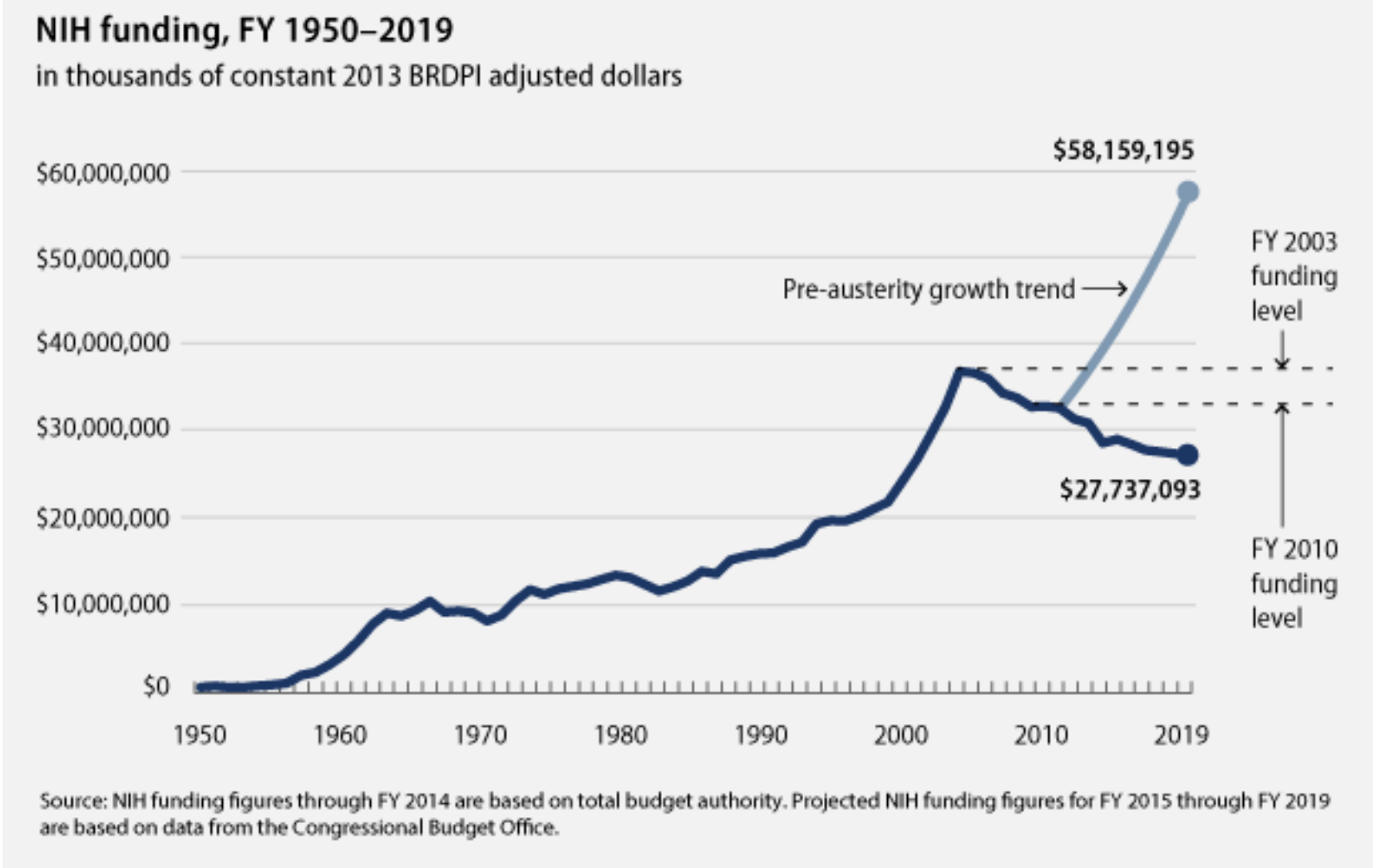
- Threats of FDA regulation could be paralyzing
- Many disorders are new, and developing understanding of disease mechanism/treatment will take time and resources for research

NIH Funding is Declining



Conclusion

- There are important opportunities to improve the health of the country and decrease health care costs and allow us to lead the world in innovation, but this will require investment to realize our potential