Precision Medicine

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PARTNERS HEALTHCARE

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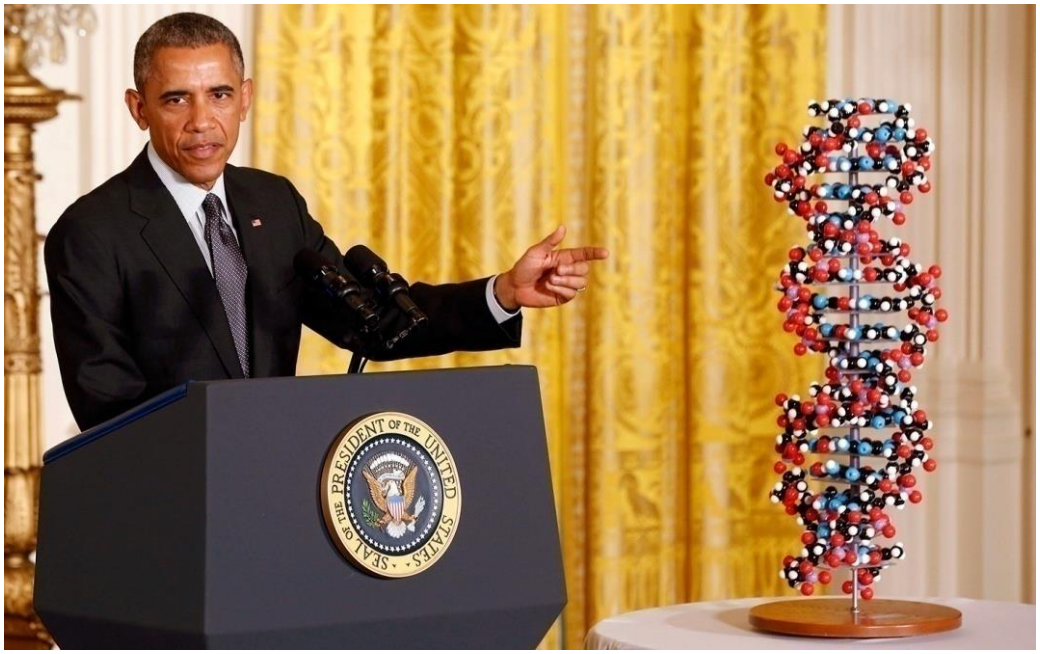
Precision/Personalized Medicine



"And that's why we're here today. Because something called precision medicine -- in some cases, people call it personalized medicine -- gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen."

"And that's the promise of precision medicine -- delivering the right treatments, at the right time, every time to the right person." (President Obama)

Sequencing the Human Genome 1990-2000

1990 - 2001

TEN YEARS – PUBLIC AND PRIVATE EFFORT – INTERNATIONAL – THOUSANDS OF PEOPLE – ESTIMATED COST $2.5 BILLION


397-387

Illumina units

Cost of sequencing highly reduced

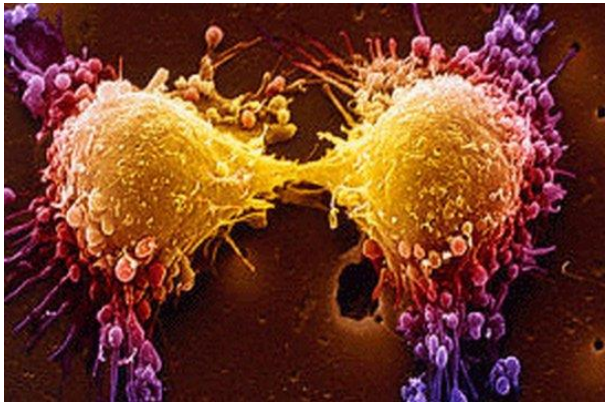
It is now possible for clinical sequencing all 22,000 genes for $1,000 or less

Oxford Nanopore sequencing unit

Role of Precision Medicine

Genetics in health and disease

Can assess risk and eliminate or reduce rare disorders



Can effectively treat many disorders including cancer

THE POWER OF GENETICS

Non-invasive prenatal diagnosis

Can diagnose molecular basis for childhood disorders

How to keep people healthy

Prevent disease
Detect disease early
Treat disease effectively

Rare Genetic Disorders

Individually rare but collectively a significant burden on the Society and Families

Tay-Sachs disease

"Tay-Sachs disease is an autosomal recessive, progressive neurodegenerative disorder which, in the classic infantile form, is usually fatal by age 2 or 3 years" (OMIM) – Carrier freq. 1/250. Irish / British Isle descent 1/50 to 1/150. French Canadians, Louisiana Cajuns and Ashkenazi Jews 1/27.

Dor Yeshorim

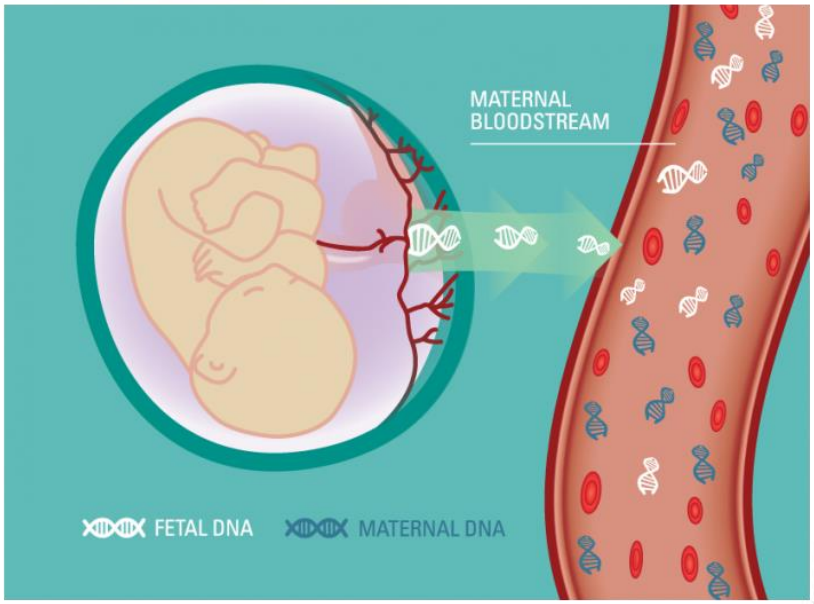
Committee for Prevention of Genetic Diseases based in Brooklyn and others locations

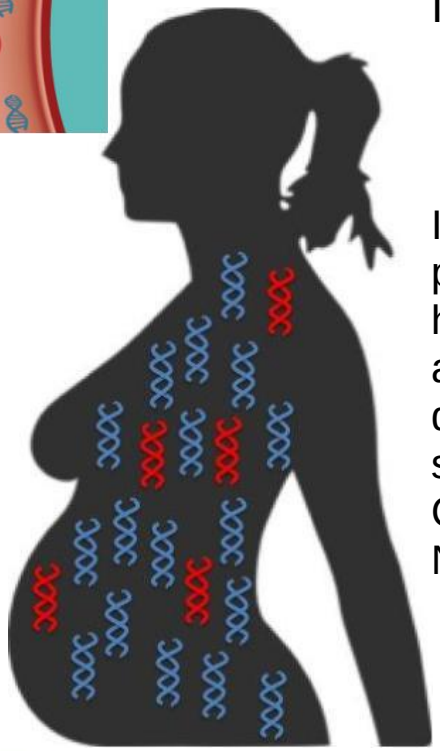
Established by Rabbi Joseph Ekstein who lost four children to Tay-sachs

Each member of the group has a 1/5 chance of being a carrier for one of 9 disorders

- **Individuals are tested during large sessions in Jewish schools and processed anonymously**
- **When couples are contemplating marriage, they can anonymously check for carrier status**
- **This approach was credited to "near total elimination" of Tay-Sachs in the population**

Fetal DNA in maternal blood (cfDNA)





Women who become pregnant after age 35 are recommended to have fetal testing using amniocentesis or chorionic villus sampling. The ability to obtain fetal DNA from maternal blood is rapidly changing the need for invasive procedures.

Bianchi et al NEJM 370:799-808, 2014

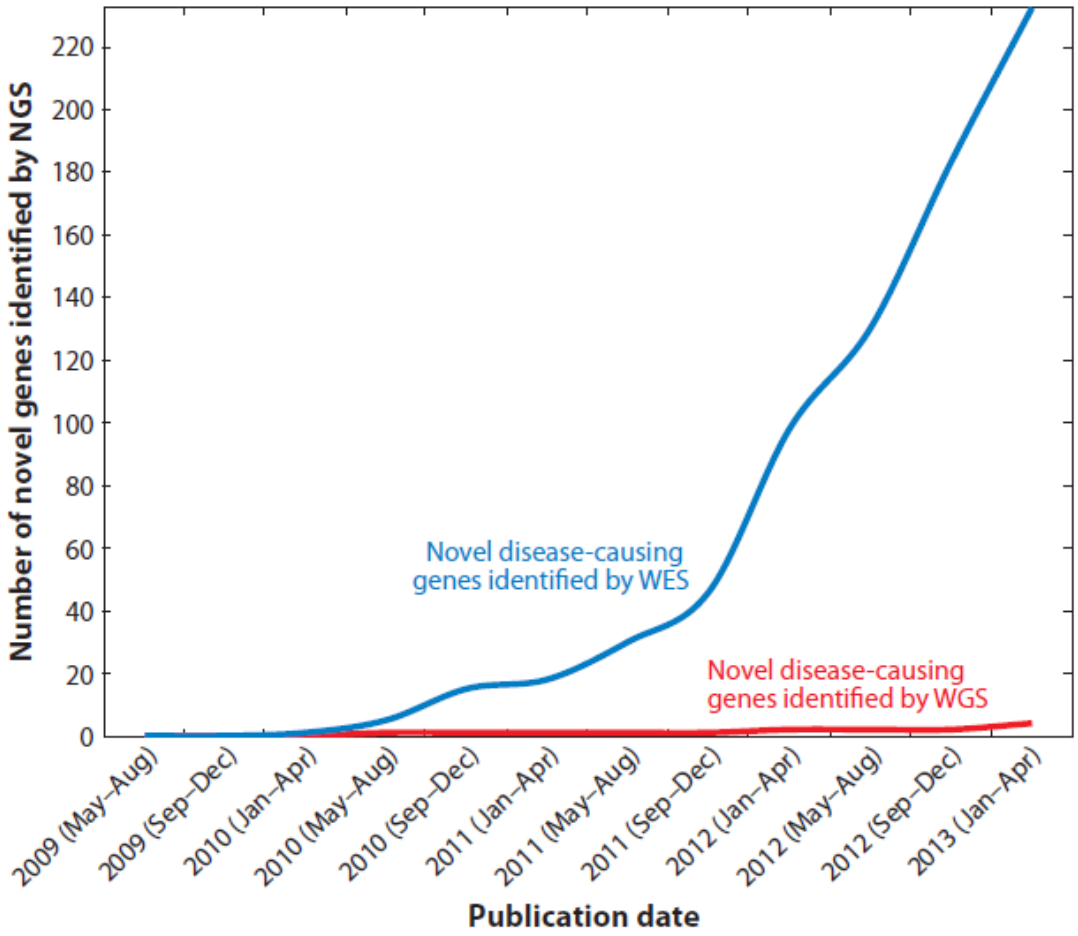
In a general obstetrical population, prenatal testing with the use of cfDNA had significantly lower false positive rates and higher positive predictive values for detection of trisomies 21 and 18 than standard screening. (Funded by Illumina; ClinicalTrials.gov number, NCT01663350.)

Nicholas Volker

Nicholas Volker's intestine had been dangerously inflamed, necessitating a hundred surgeries including the removal of his colon. Based on DNA sequencing it was possible to identify two genetic mutations. 1. XLP: X-linked lymphoproliferative and 2. a gut disease that has not been described before. XLP can be treated by a bone marrow transplant of cells taken from umbilical cord blood. Nicholas is doing well, although he still takes drugs to prevent transplant rejection and will need more reconstructive surgery.

Nicholas in 2013

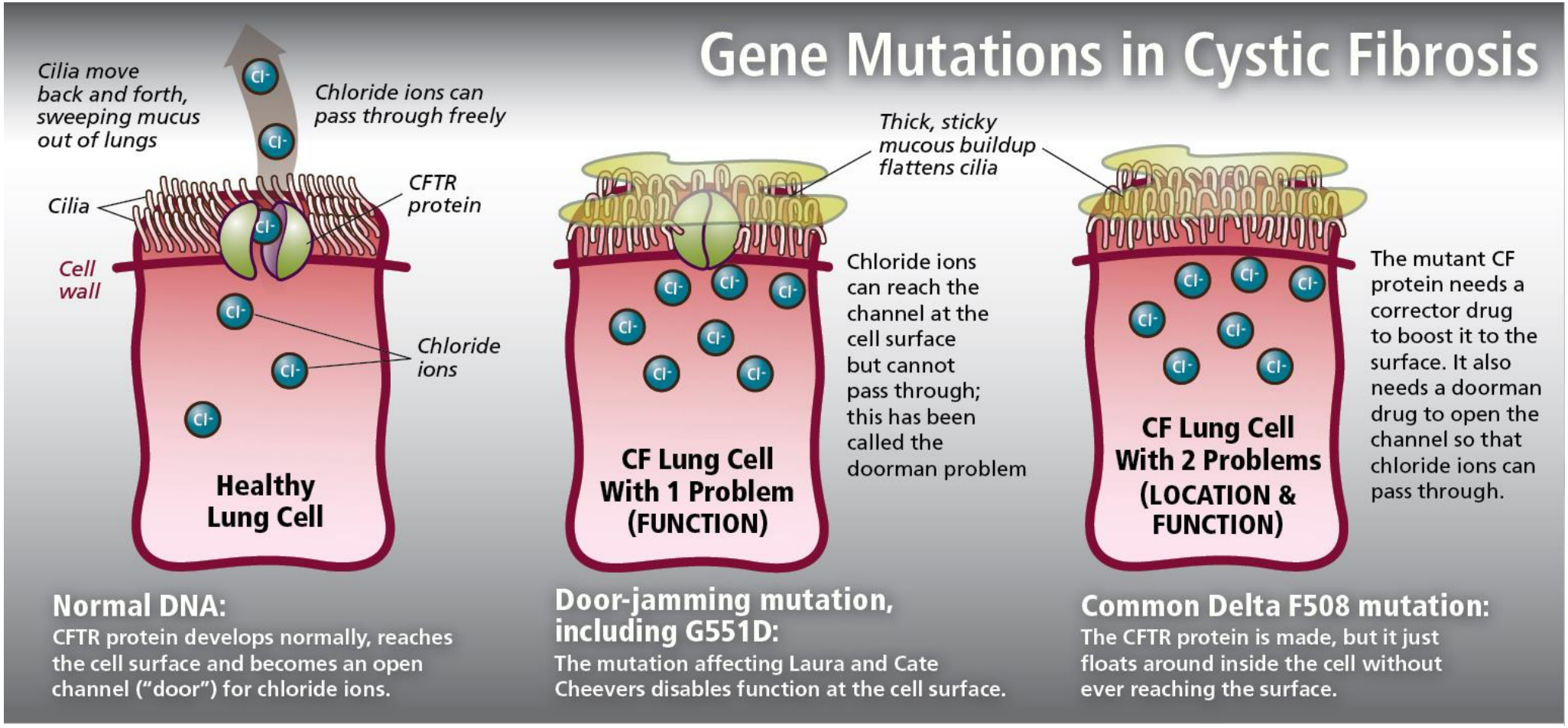
Genes involved in childhood disorders



From Boycott etal Ann. Rev. Med. 65:19-31. 2014

- >7,000 rare genetic diseases
- 70% effect children
- Millions of children affected
- Diagnostic Odessey
- Waited 5-30 years for Dx
- 40% wrong diagnosis at the beginning
- In 30% of cases WES can identify a gene and can lead to Dx
- Dx dictates treatment

Cystic fibrosis (CF)

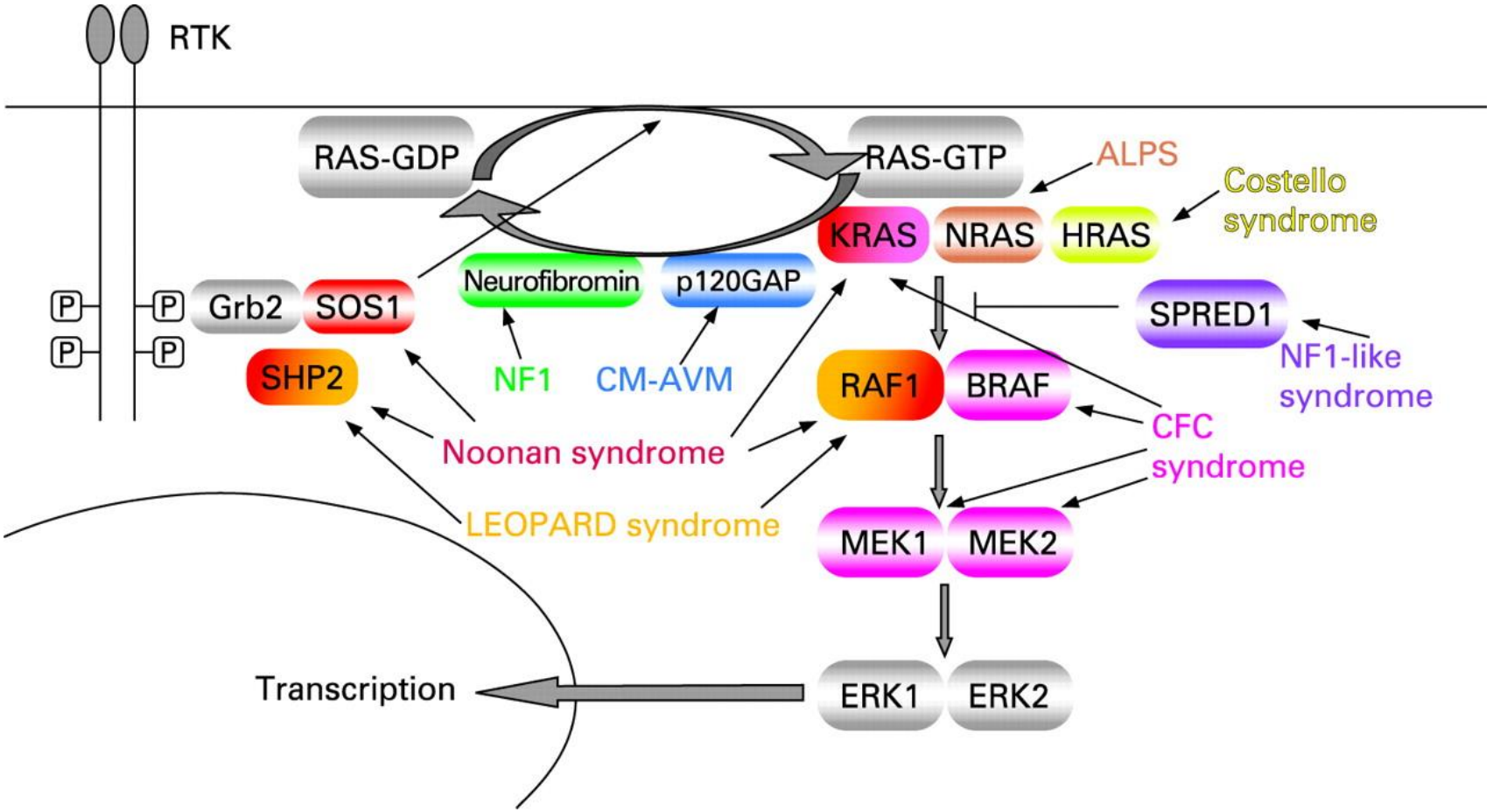


Cystic fibrosis treatment

Gaucher's disease

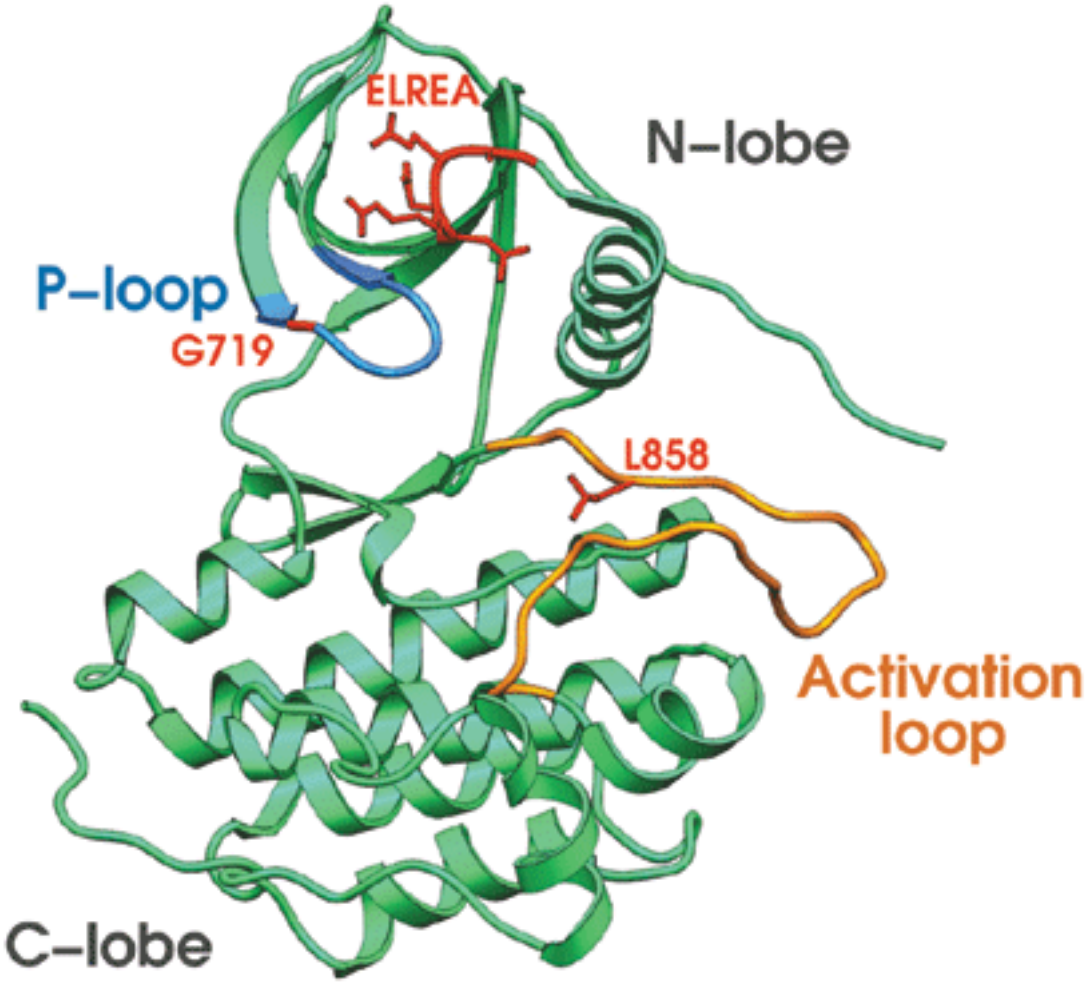
The Path from Genetic Discovery to Patient Care

Opportunities for Drug Development
Noonan syndrome and many others



Drug Development based on Gene Discovery

EGFR Mutations and TKIs for NSCLC

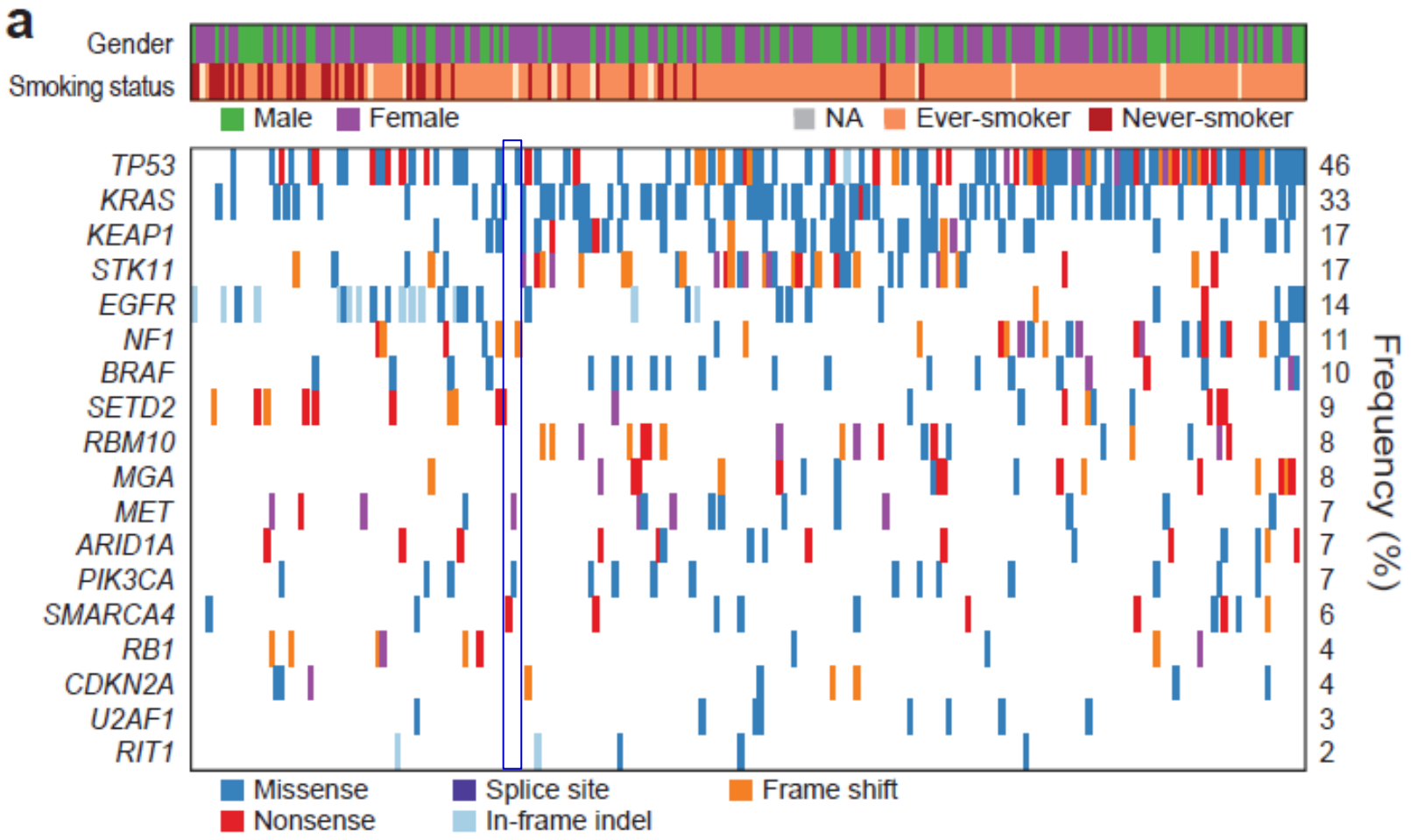


Iressa approved in the EU with genetic test.

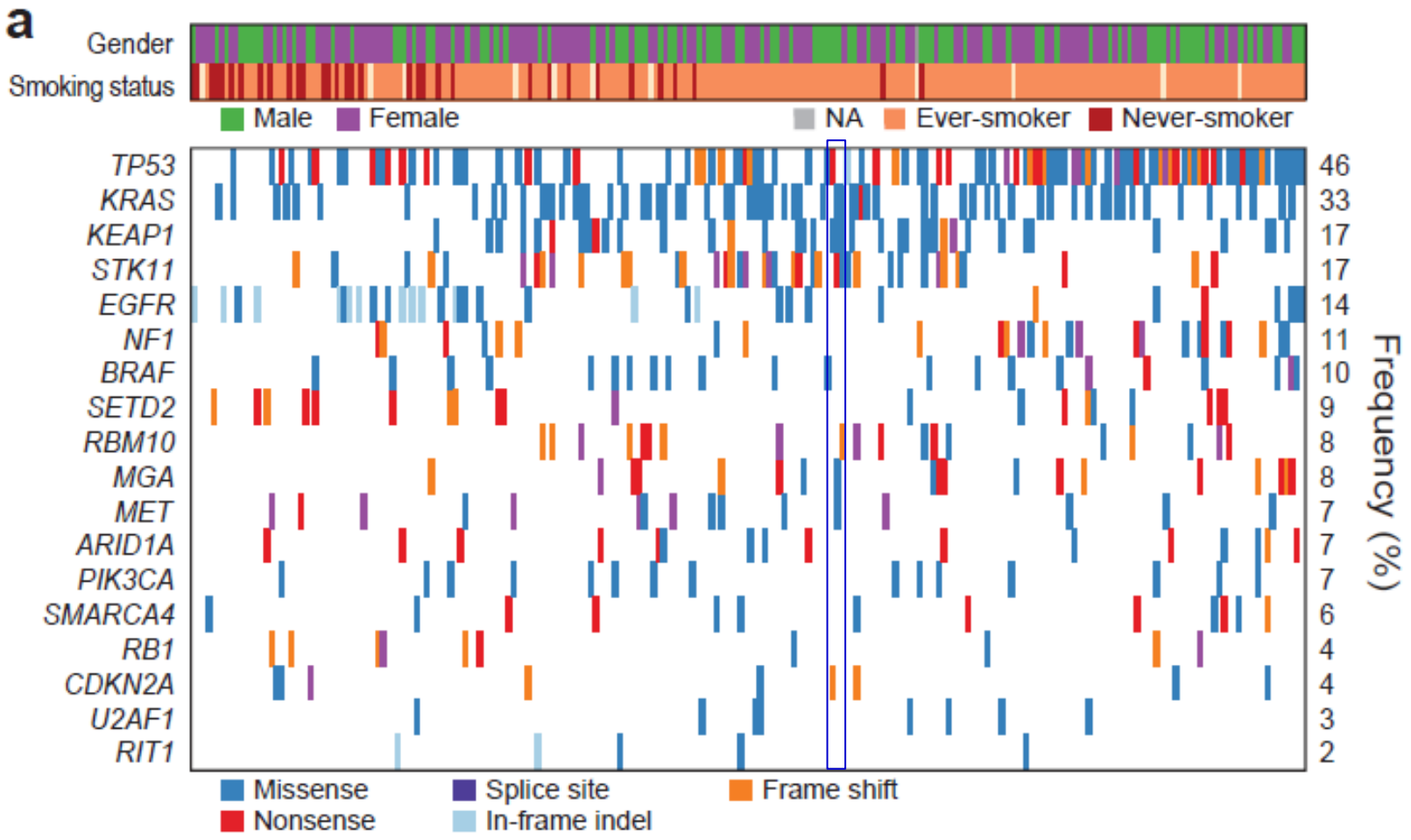
Tarceva approved in EU for first line therapy with test

EML-ALK translocations and drugs

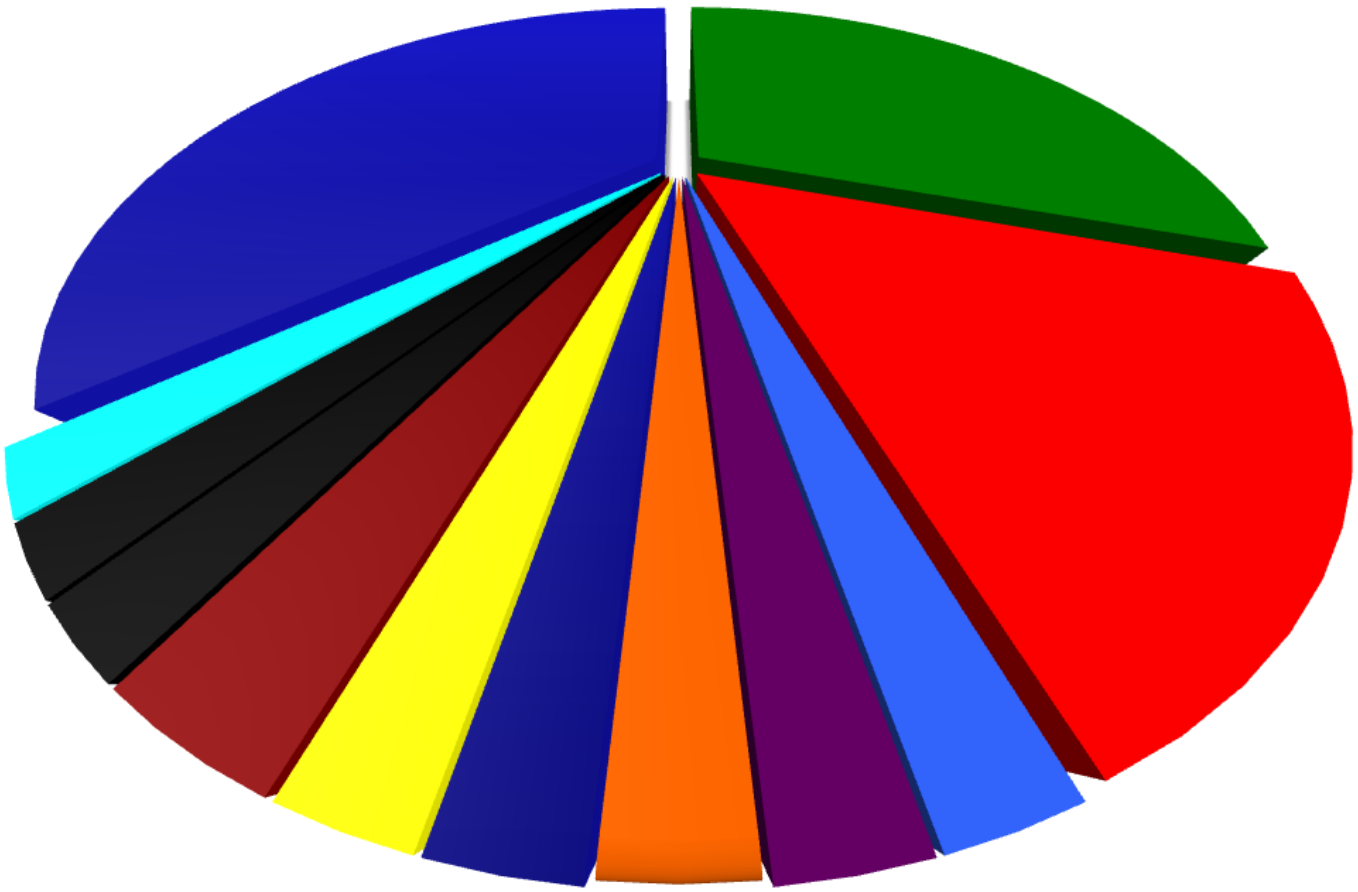
NSCLC - Adenocarcinoma



NSCLC - Adenocarcinoma



Genetic changes in non-small cell lung cancer



- KRAS mutations
- EGFR mutations
- BRAF mutations
- PIK3CA mutations
- ERRB2 mutations
- NRAS mutations
- MEK1 mutations
- ALK rearrangements
- ERRB2 amplification
- MET amplification
- RET/ROS1 gene fusions
- Other

Targeted therapies for all of these genetic alterations are approved or in development

Our experience

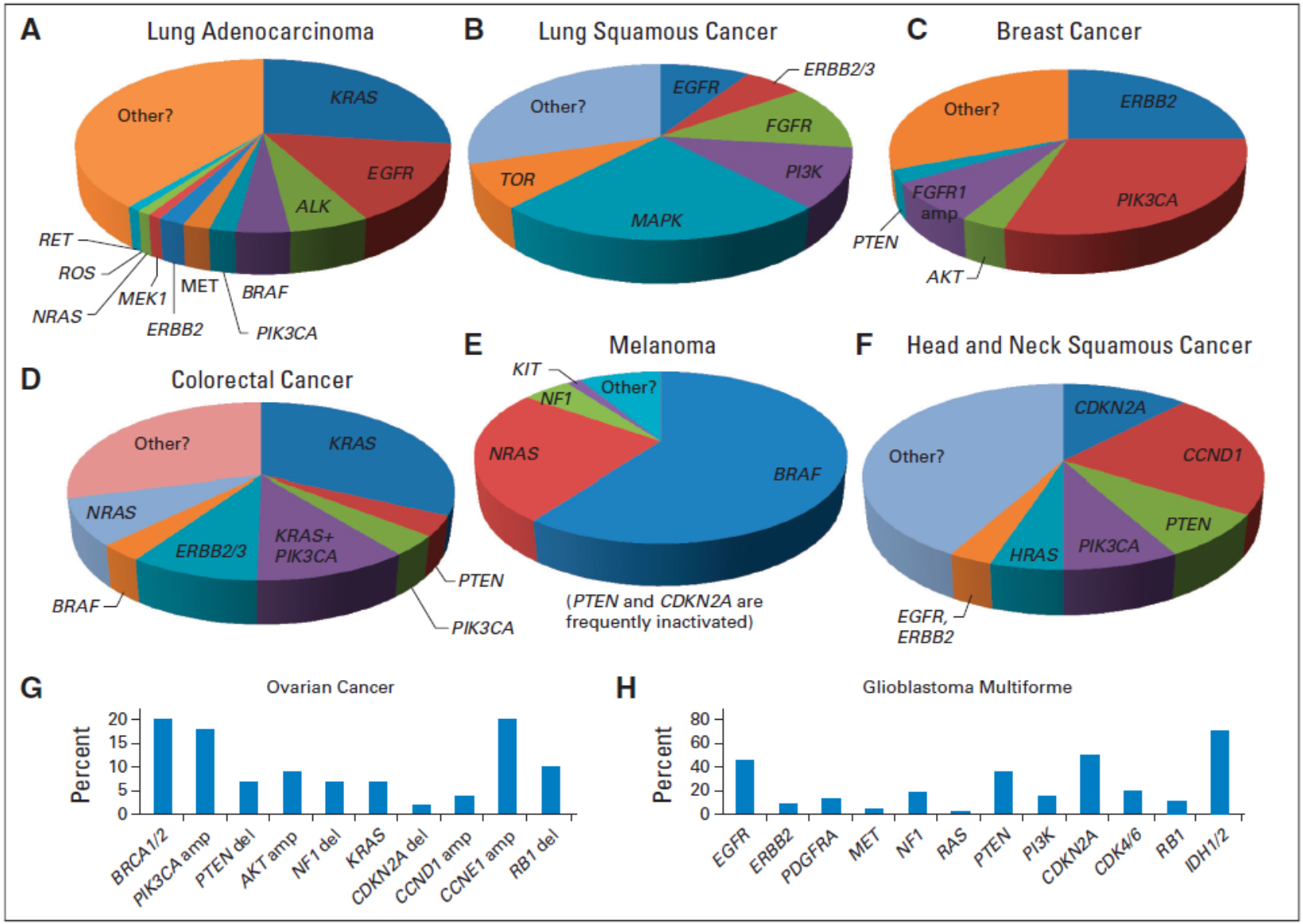
- AT Dana Farber and Brigham and Women's Hospital, every new cancer patient is receiving a genetic profile using a 380 gene panel.
- A separate heme malignancy panel of 90 genes.
- We have tested more than 17,000 patients.
- All clinical decisions are based on profiling data.
- 90% of the results are actionable.

Genetic testing is important
Dr. Wartman's leukemia

FLT3 overexpression and use of Sunitinib (NY Times July 8, 2012)

Gina Kolata

Genomic Alterations in Actionable Pathways

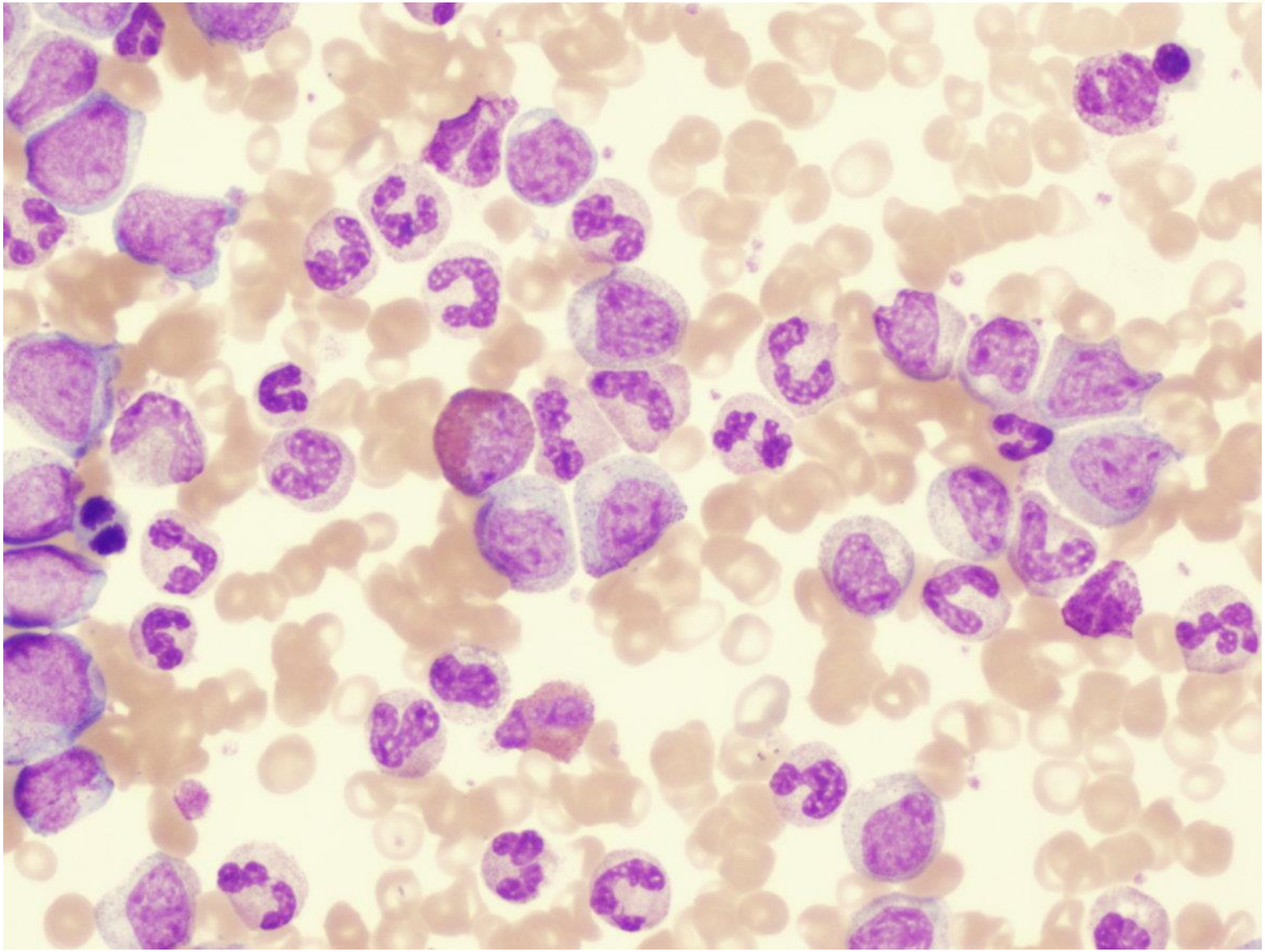


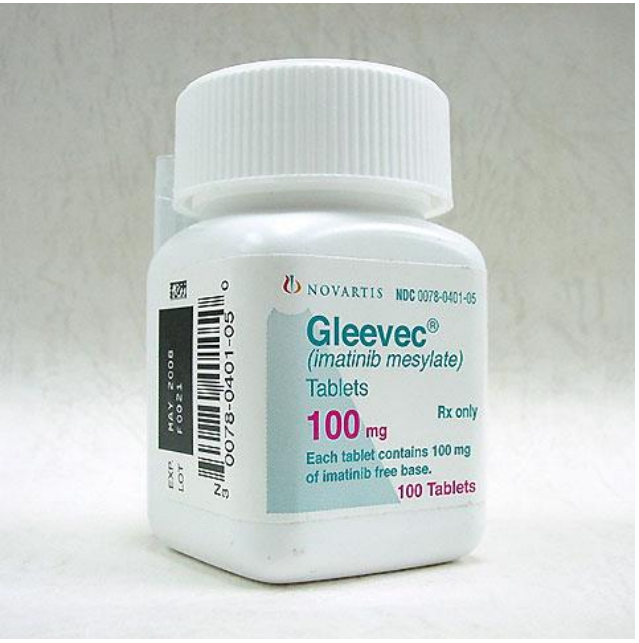
Garraway JCO 31: 1806-1814 2013

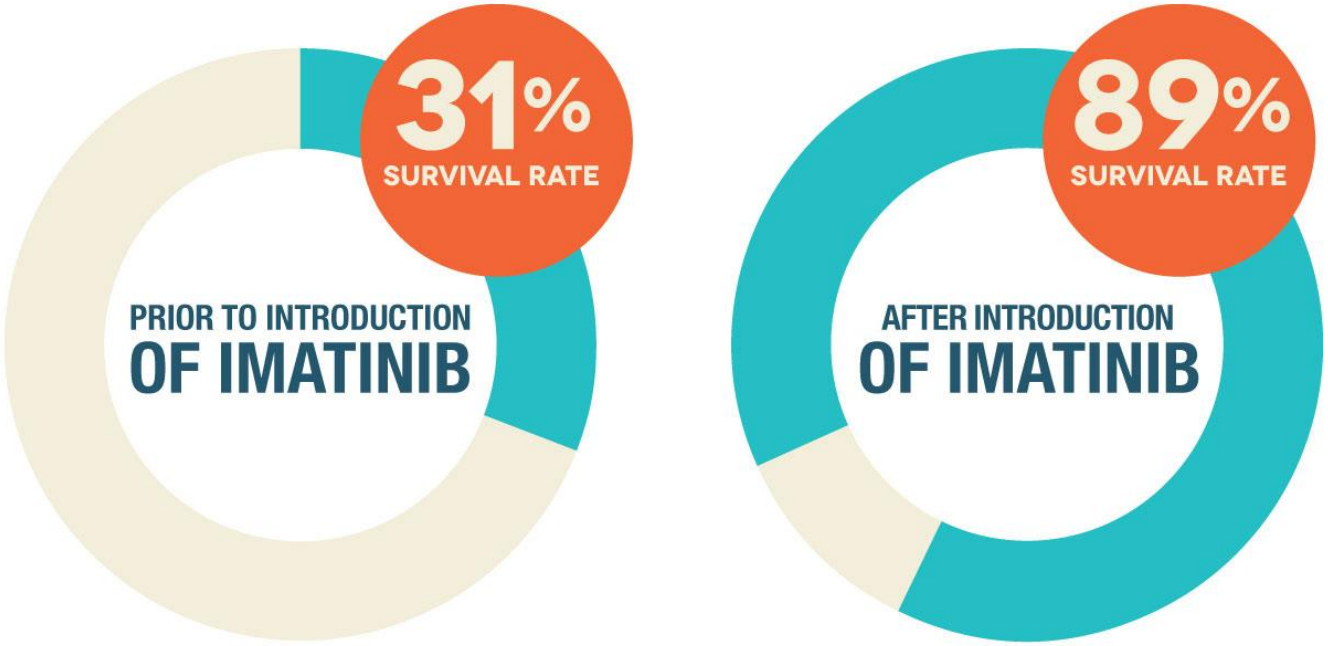
FDA Approved Targeted Drugs Are Rapidly Increasing

70% of cancer drugs in development have a biomarker

Chronic Myelogenous Leukemia (CML)







5-YEAR SURVIVAL RATE FOR CML PATIENTS

Introduced in 2001
2012 revenues 4.7 BB
Patients diagnosed with CML are now having normal life spans

Future for Precision Medicine

- Scientific knowledge about the role of genetics in many disease is increasing rapidly
- This knowledge is leading to development of novel drugs and therapies
- Continued reductions in cost of DNA sequencing is making genetic testing more affordable
- It is likely that genetic/genomic testing will play a more important role in cancer drug development and patient care