Molecular Advances in MDS

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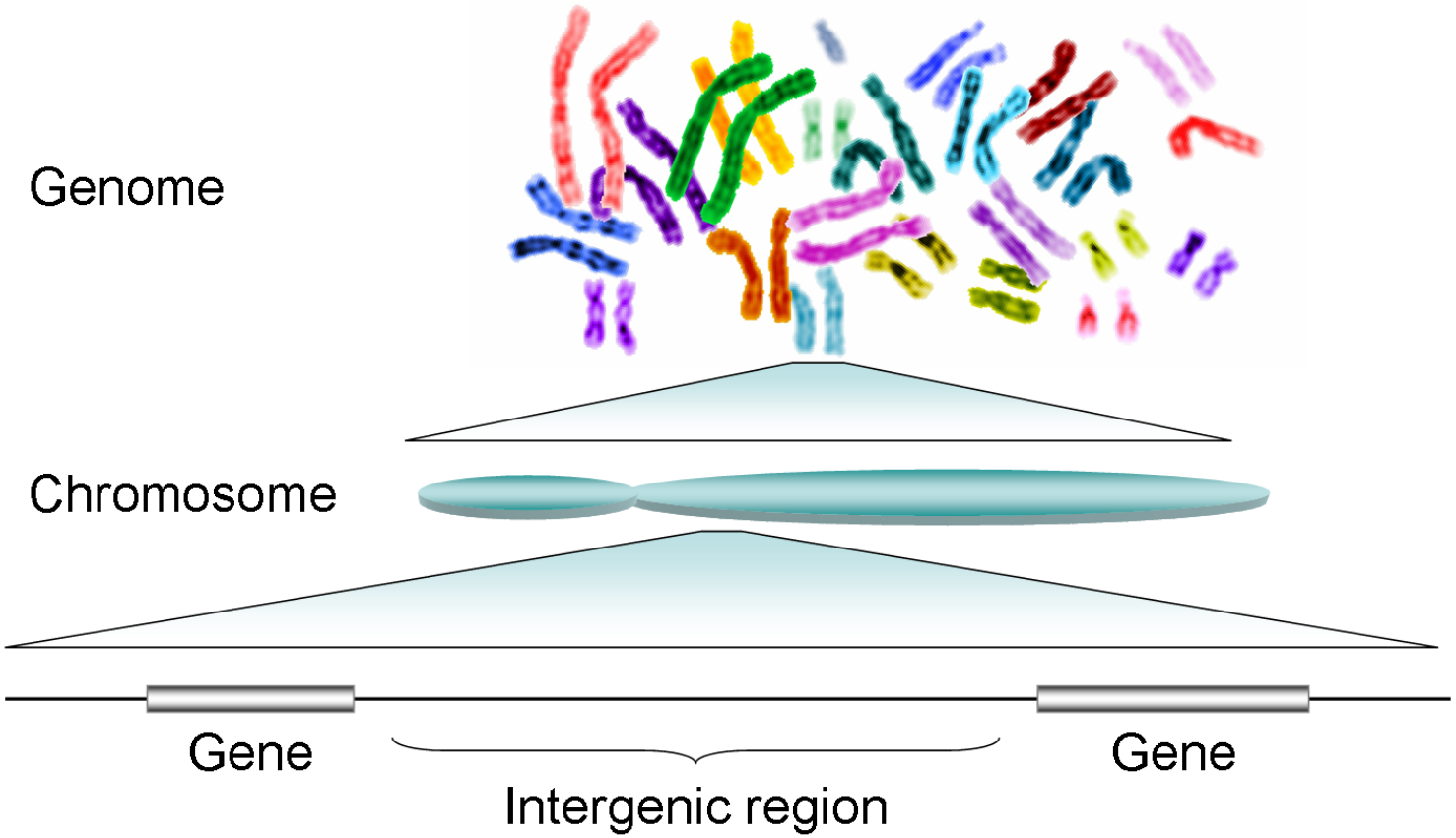
Learning Objectives

- Next Generation Sequencing
- MDS Genomics
- Hereditary MDS
- Future Directions

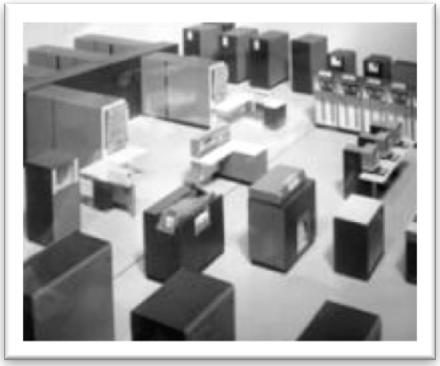
Genes, Genomes, Mutations



Normal: ATCCCGACTTGCCTGTAAAATCCAAA
Mutation: ATCCCGACTTGCC**C**GTAAAATCCAAA

Sequencing: Disruptive Technology

Main Frame



Mini Computer

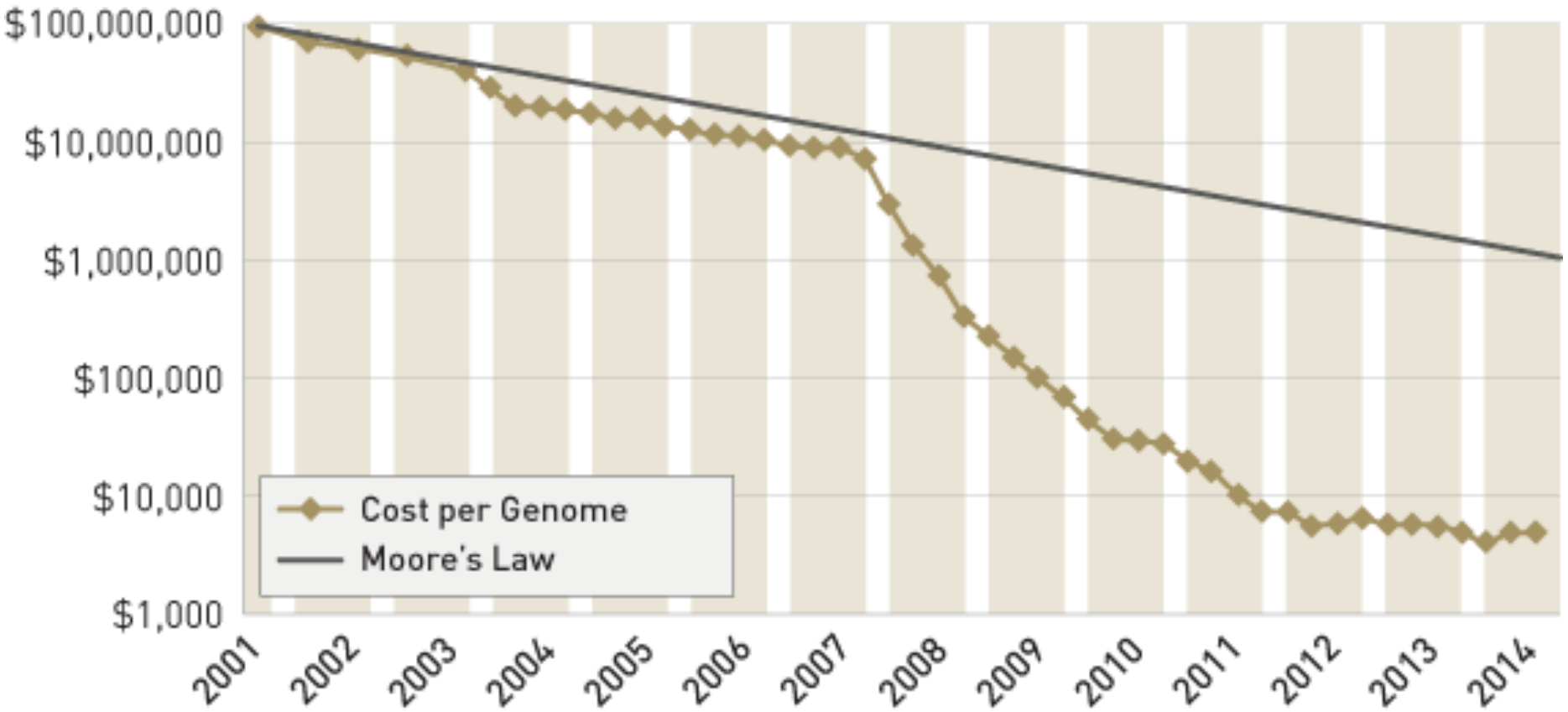
Personal Computer

Gel Based Sequencing

Sanger Sequencing

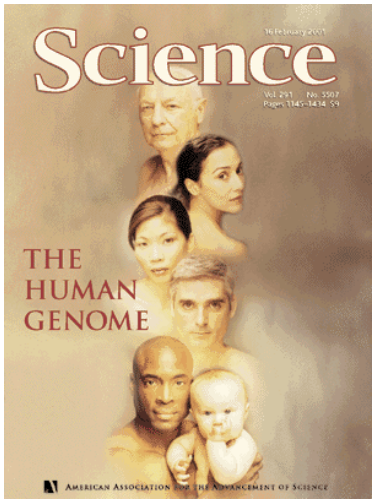
Next Generation Sequencing

Sequencing Costs Have Plummeted



Forbes , 2010

An Explosion in Genetic Knowledge



Massive Genomics Research

Thousands of genomic associations, many with clinical implications

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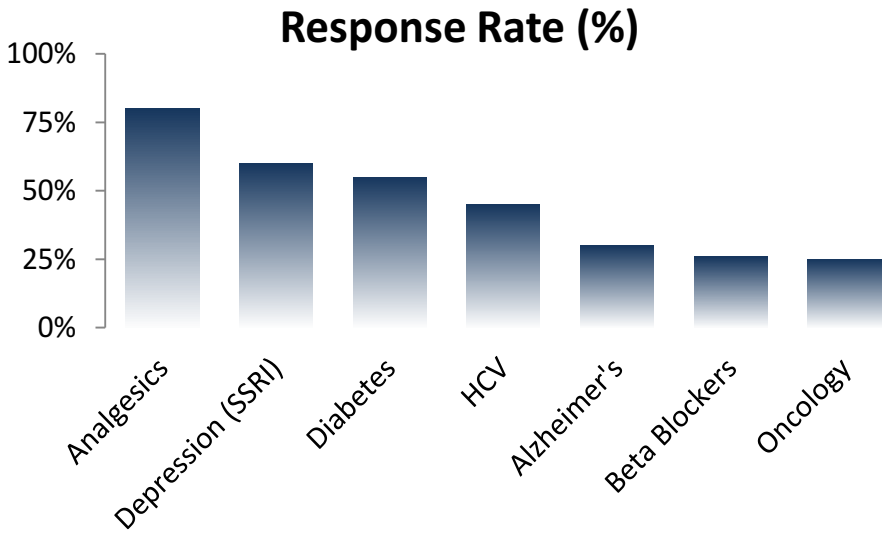
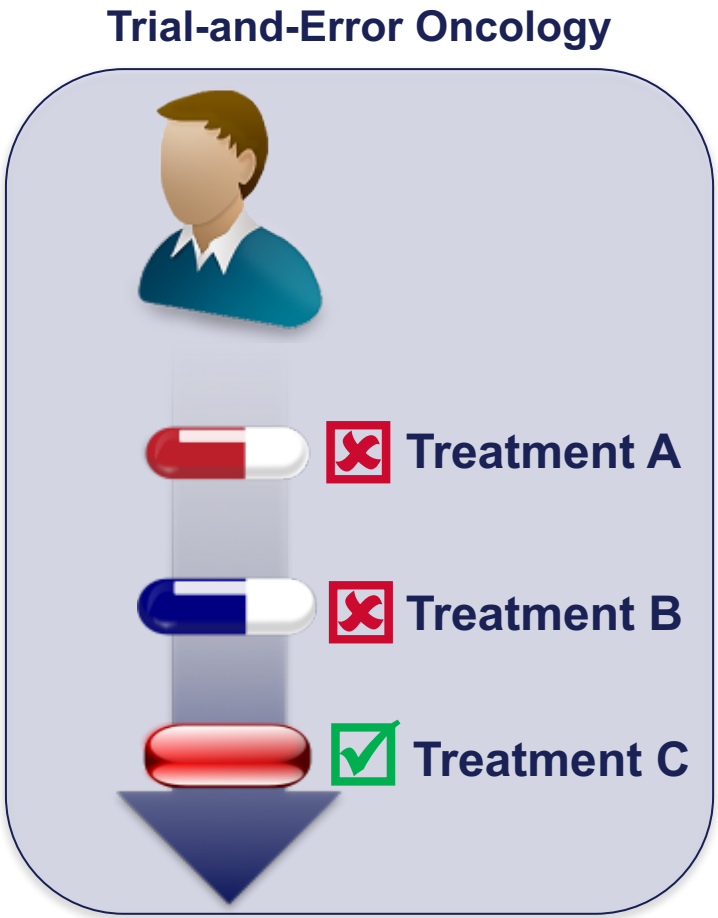
Hematology / Oncology: An Imperfect Art



Given limited ability to predict responders, doctors today practice trial-and-error medicine

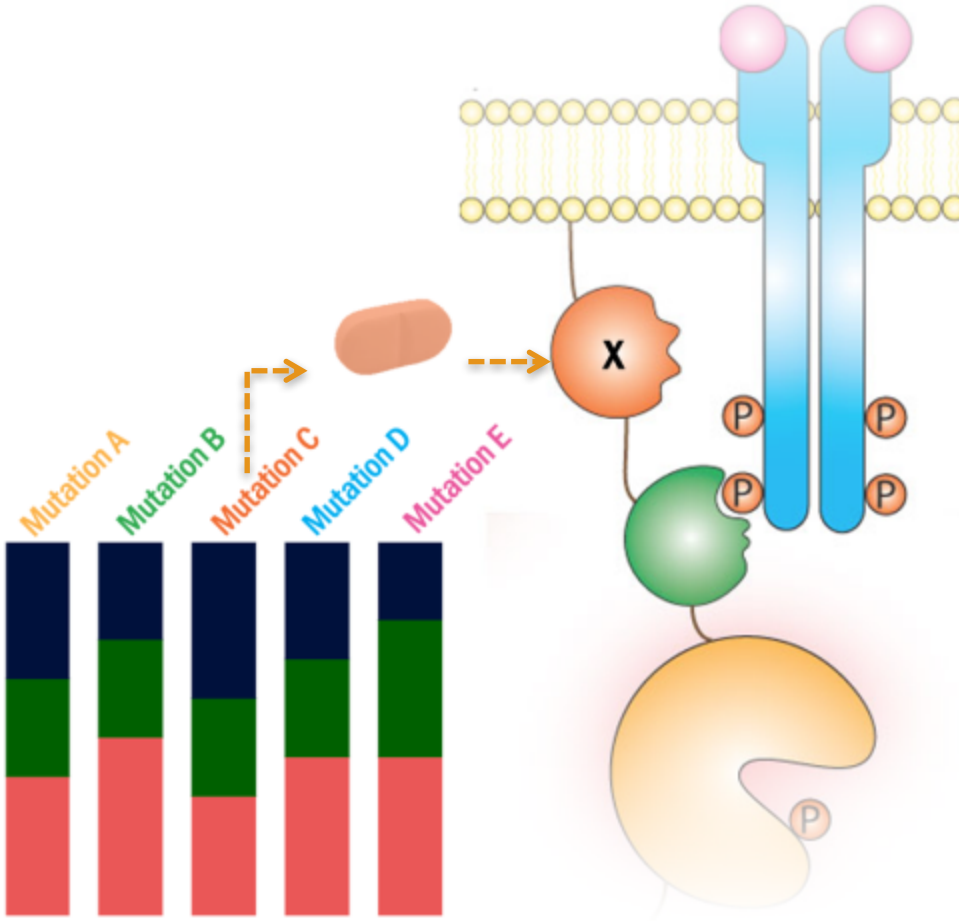


Adapted from: Spear et al. TRENDS in Molecular Medicine Vol.7 No.5 May 2001; PMC Nov 2006

The Solution: Personalized Medicine

"**Personalized medicine**" refers to the tailoring of medical treatment to the individual characteristics of each patient …[by the] ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.

Traditional Classification



Genomic Classification

Adapted from: Aleshin A et al. Neoplasia. 2010

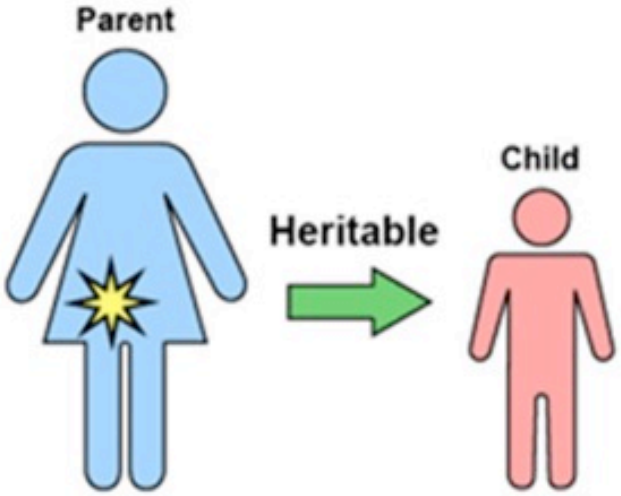
Two Sides of Mutations

Somatic mutations
- Occur in ***nongermline*** tissues
- Cannot be inherited

Nonheritable

Mutation in tumor only

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome



Mutation in egg or sperm

All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology

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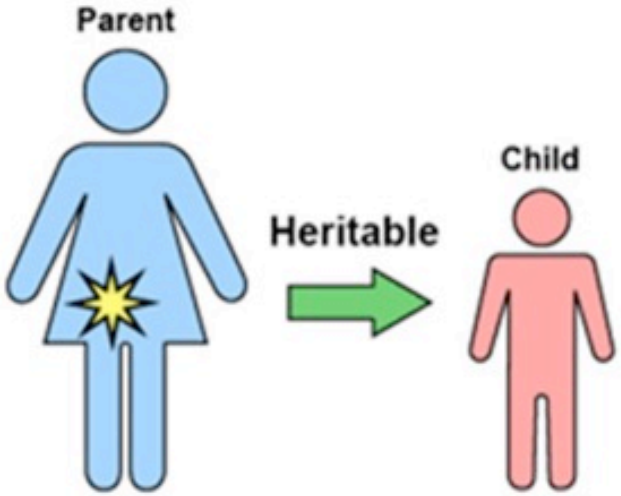

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Adapted from the National Cancer Institute and the American Society of Clinical Oncology

MDS is Genetically Not One Disease …

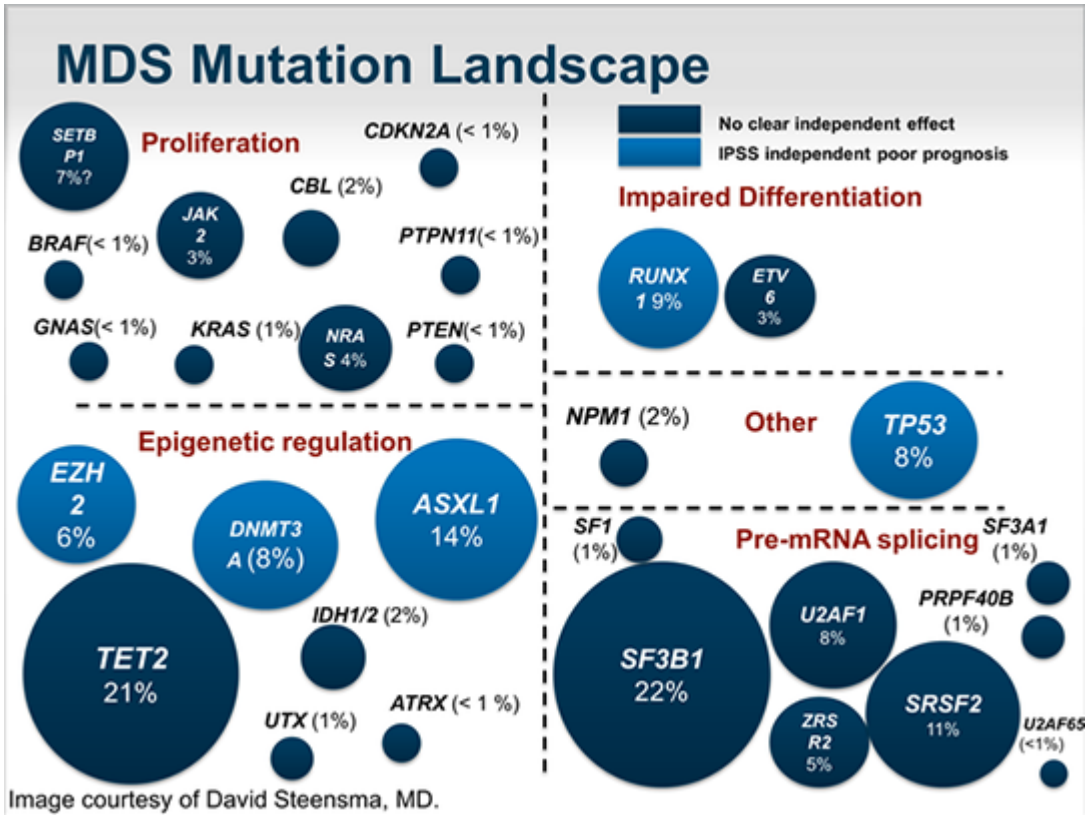
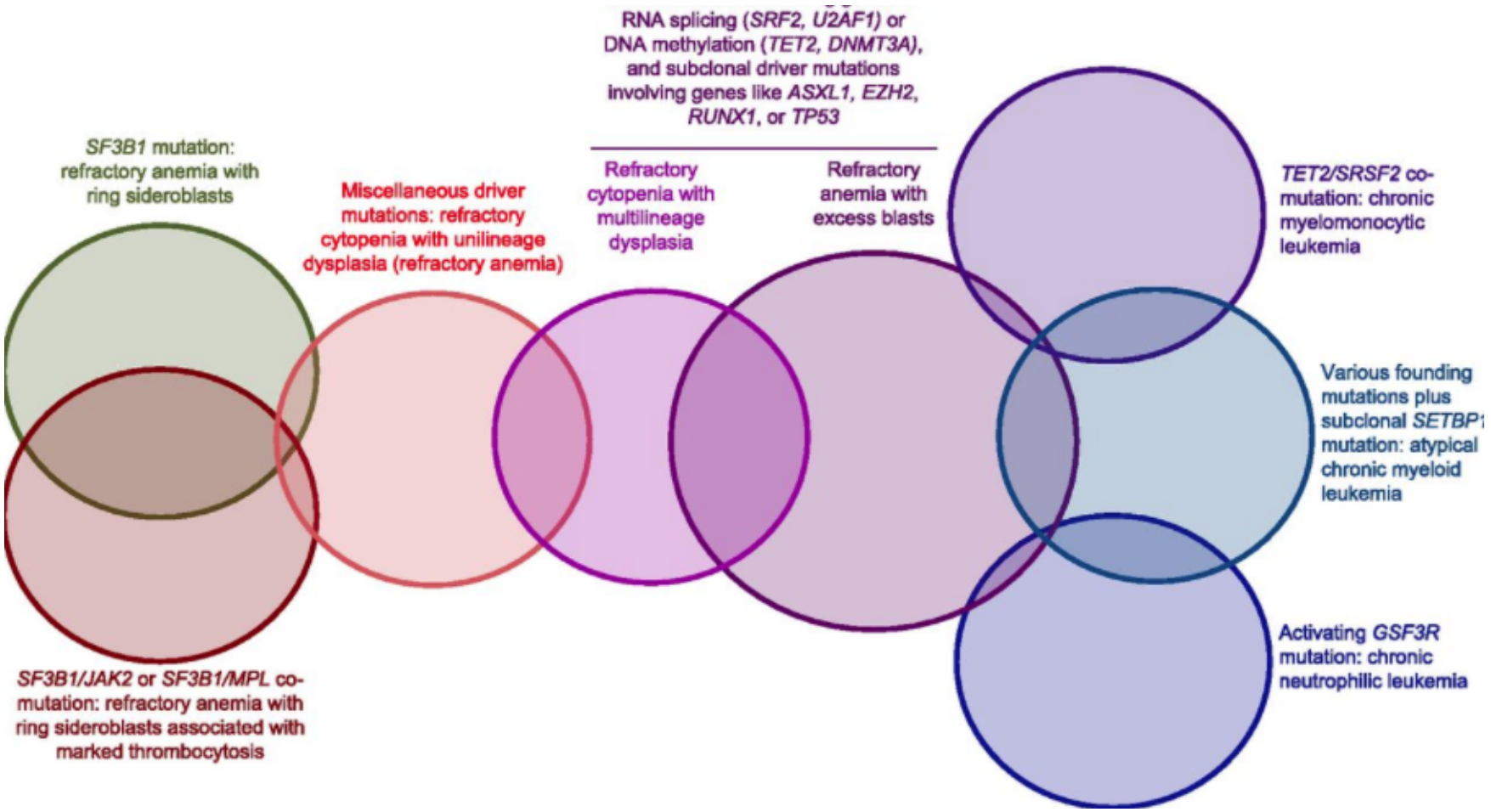


Image courtesy of David Steensma, MD.

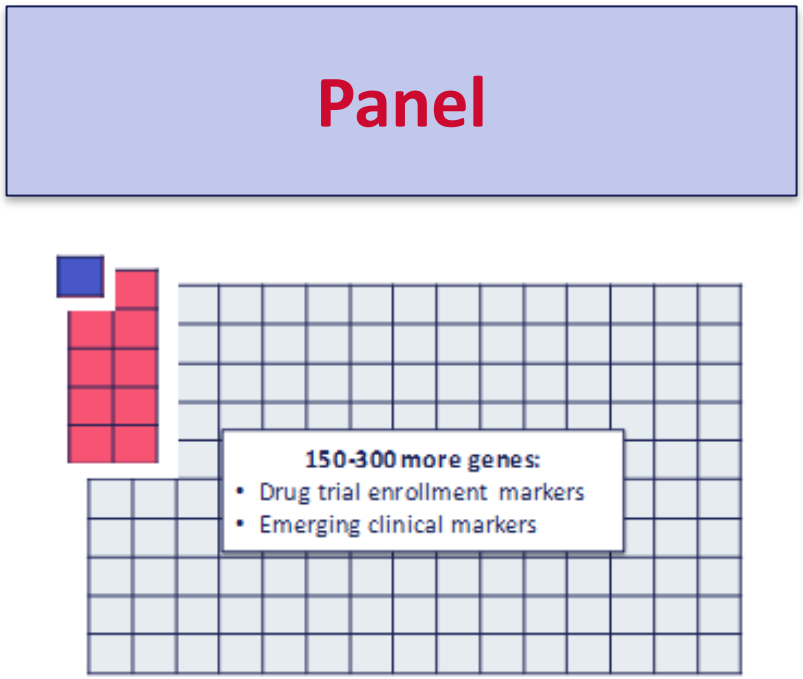
Mutations Cluster with MDS Subtype



Adapted from: Cazzola et al, Blood 2013

How Do We Identify These Mutations?

Panels vs Single Gene



1. Test for Known Mutations

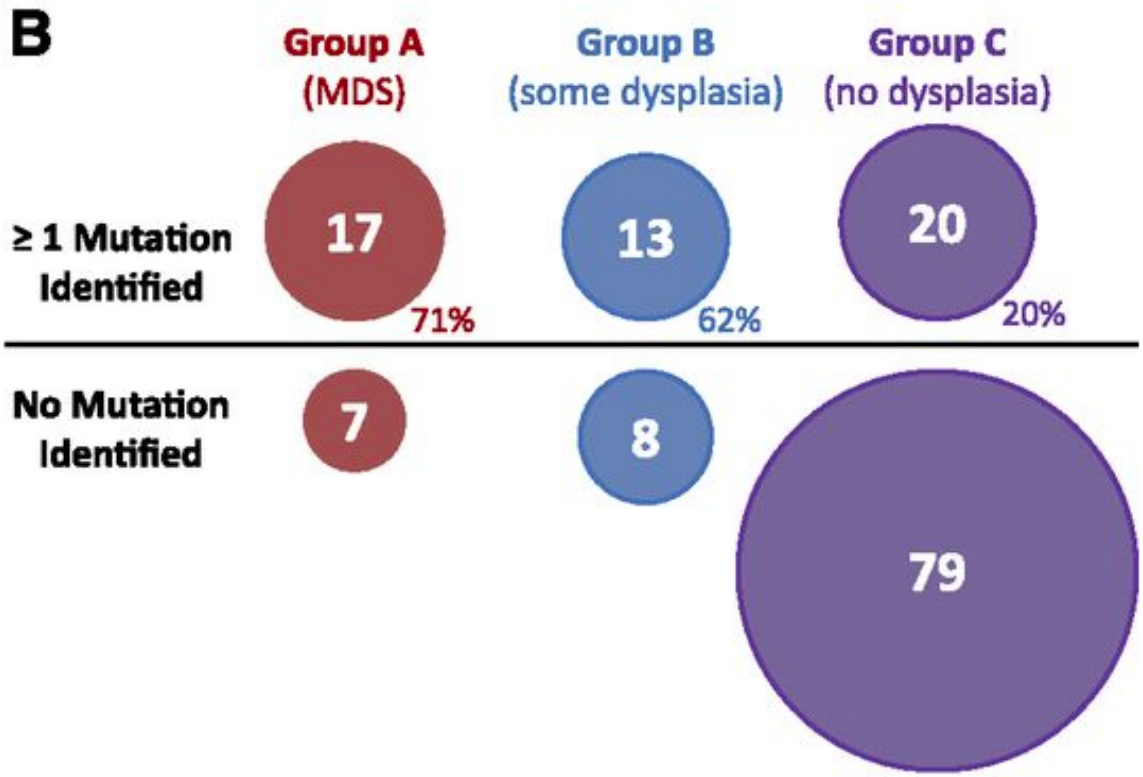
- Mutations discovered through GWAS, exome, WGS studies

2. Fast turn around time

Molecular Diagnostics in MDS – Possible Uses

- Support / Refine Diagnosis
  - MDS with ring sideroblasts when number of ring sideroblasts < 15%
- Risk Stratification
  - Better refine risk for progression to AML or higher risk MDS
- Identify Potential Therapeutic Targets
  - IDH2 mutations -> enasidenib (Idhifa)
- Monitor Disease over Time
  - Identify evidence of clonal evolution
  - Detect emergence of high risk clones

Support / Refine Diagnosis

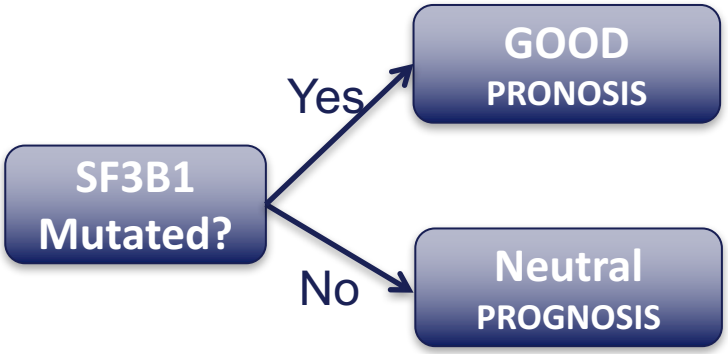


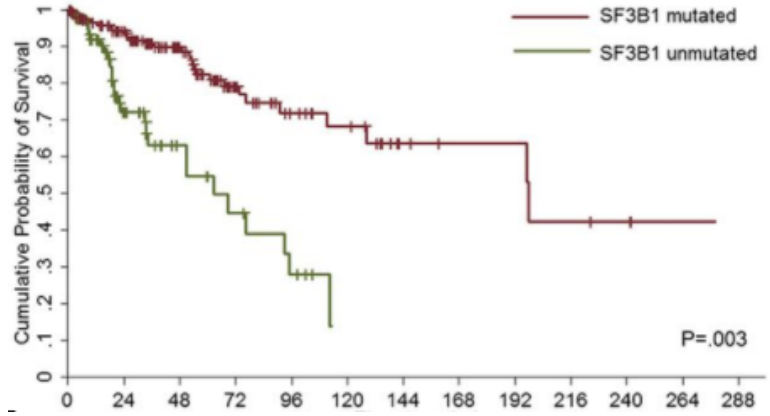
Adapted from: Kwok et al, Blood 2015

Risk Stratification

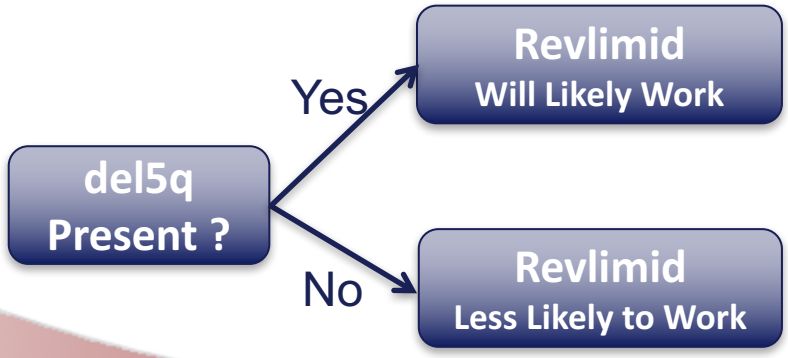
(Different from Treatment Selection)

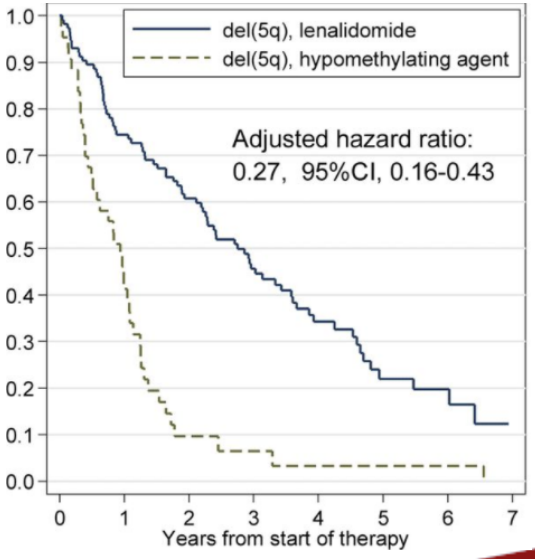
- Many mutations are **PROGNOSTIC**





- So far **ONLY FEW** are **PREDICTIVE** of treatment response

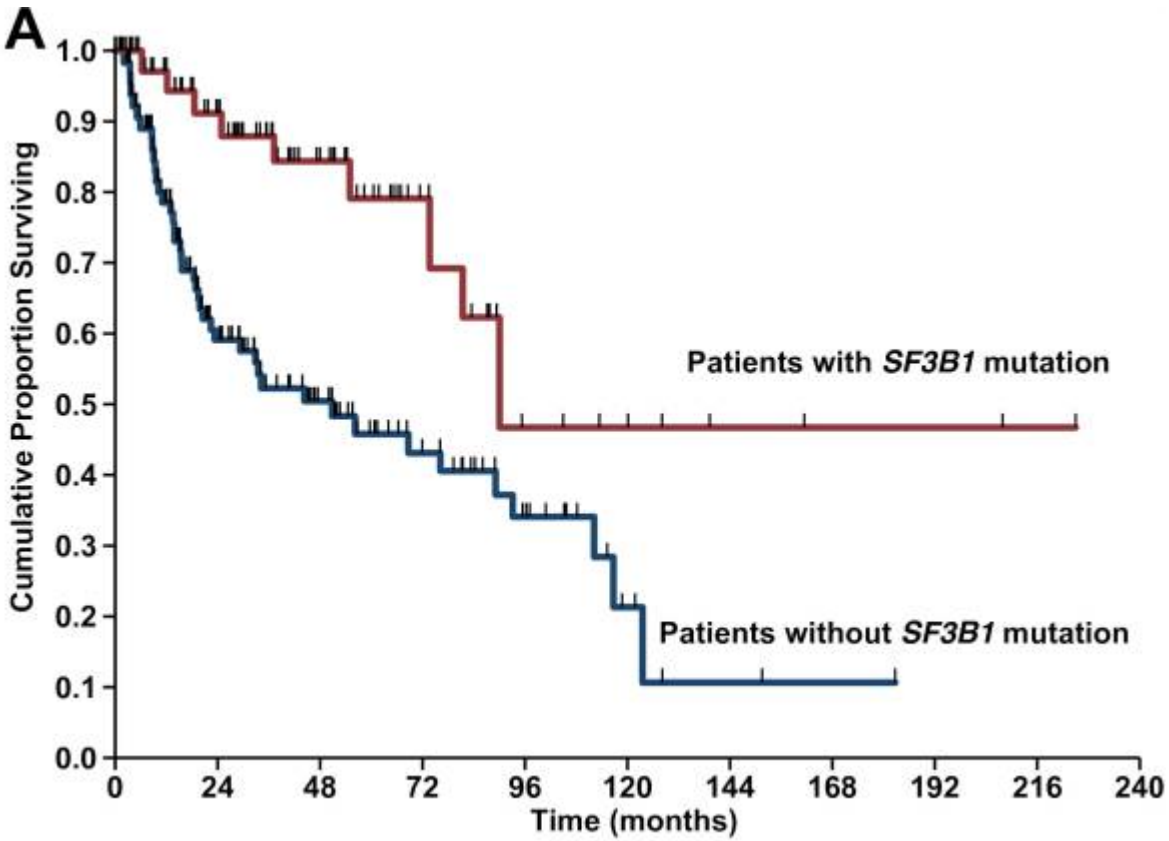




Adapted from: Malcovati et al, Blood 2015. Reagan et al, Blood 2016

Risk Stratification

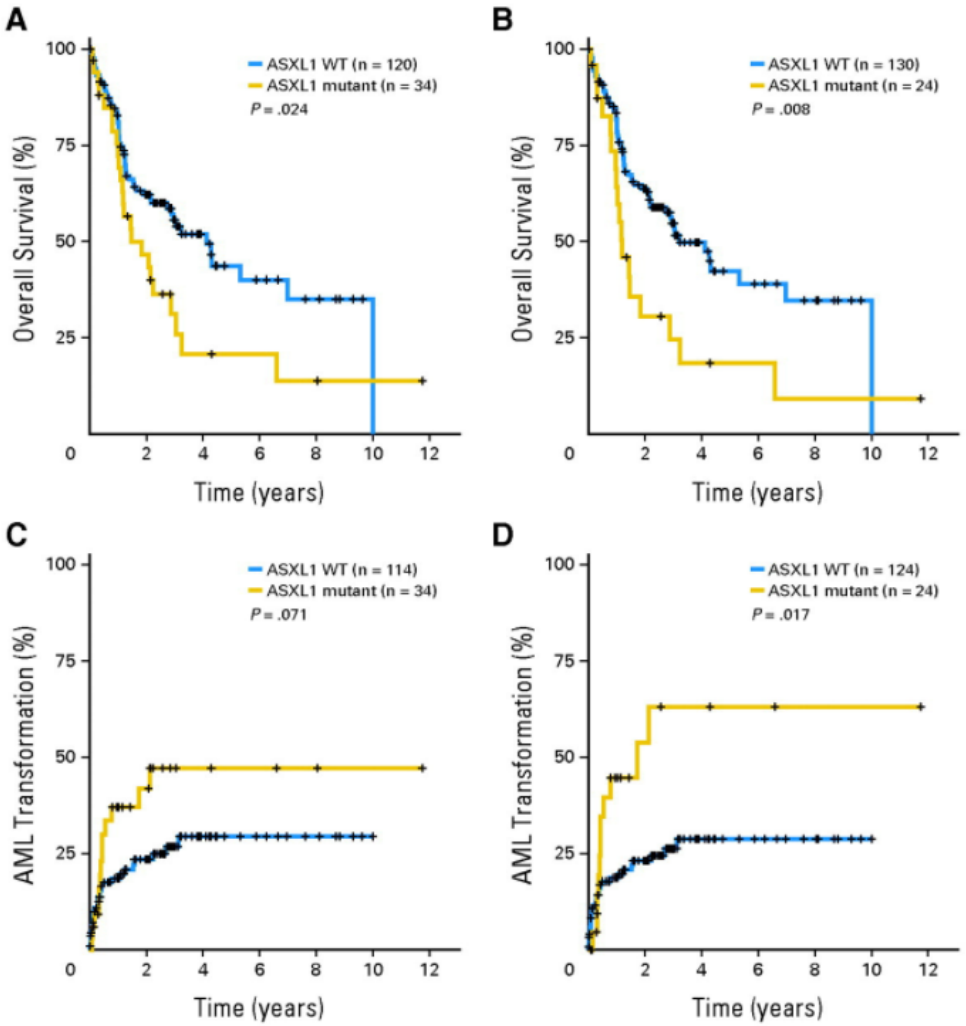
SF3B1 Mutation and Favorable Prognosis



Blood. 2011 Dec 8; 118(24): 6239–6246.

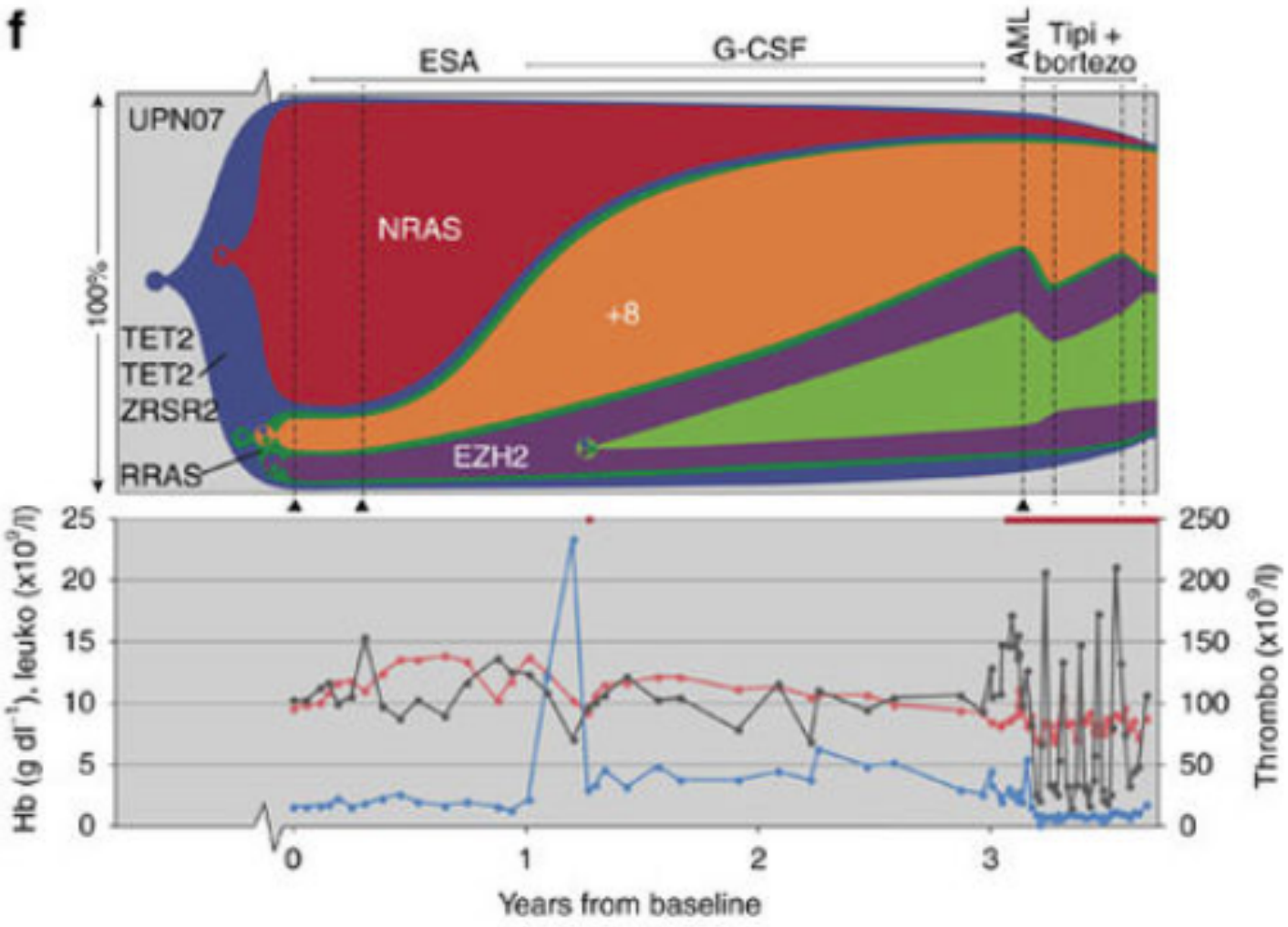
Risk Stratification

ASXL1 Mutation and Worse Prognosis



Thol et al, JCO 2011

Disease Monitoring



Adapted from: Da Silva-Coelho et al, Nature Communications. 2017

Treatment Selection

- Splicesome mutation -> H3B-8800 splicesome inhibitor
- SF3B1 -> trial of luspatercept
- del 5q - > lenalidomide

Adapted from: Coombs et al, Nat Rev Clin Oncol. 2016

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Two Sides of Genetics … Hereditary

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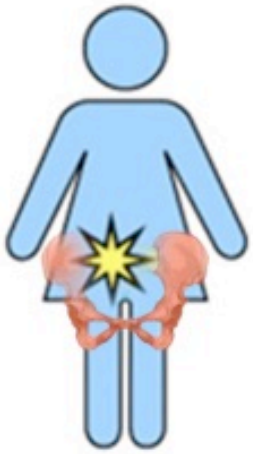

Nonheritable

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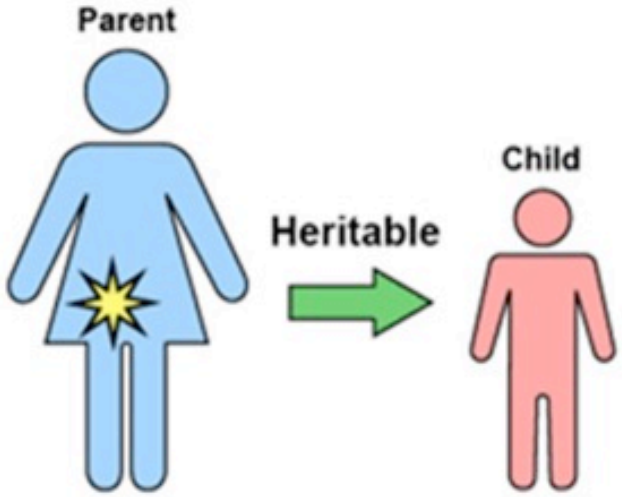

Mutation in egg or sperm

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Adapted from the National Cancer Institute and the American Society of Clinical Oncology

All Cancer is Genetic…

…But only 10% is inherited

Hereditary Syndromes w/ Predisposition to MDS

- Familial MDS/AML syndromes
- Inherited Bone Marrow Failure Syndromes
- Familial cancer predisposition syndromes with increased risk for MDS/AML (BRCA1/2, TP53, etc)

Disorders rare, but increasingly being recognized and tested for in clinic

Adapted from: NCCN, V 1.2018

Benefits of Testing

- Modify cancer surveillance options and age of initial screening
- Suggest specific risk-reduction measures (*e.g.* considering early bone marrow transplant)
- Clarify and stratify familial cancer risks, based on gene-specific cancer associations, such as risk for colon cancer and sarcomas in Li-Fraumeni syndrome associated with TP53 mutations
- Offer treatment guidance (e.g. avoidance of radiation-based treatment methods for individuals with a*TP53* mutation)
- Identify other at-risk family members
- Provide guidance with new gene-specific treatment options and risk reduction measures as they emerge

Red Flags: If you or family member have one of these …

- Pulmonary alveolar proteinosis
- Congenital deafness
- Hereditary lymphedema
- Skin and nail changes
- Sensorineural deafness
- Pulmonary fibrosis
- Neurofibromatosis
- Predisposition to opportunistic infections
- Multiple family members with MDS or AML
- Premature hair graying
- Thumb hypoplasia

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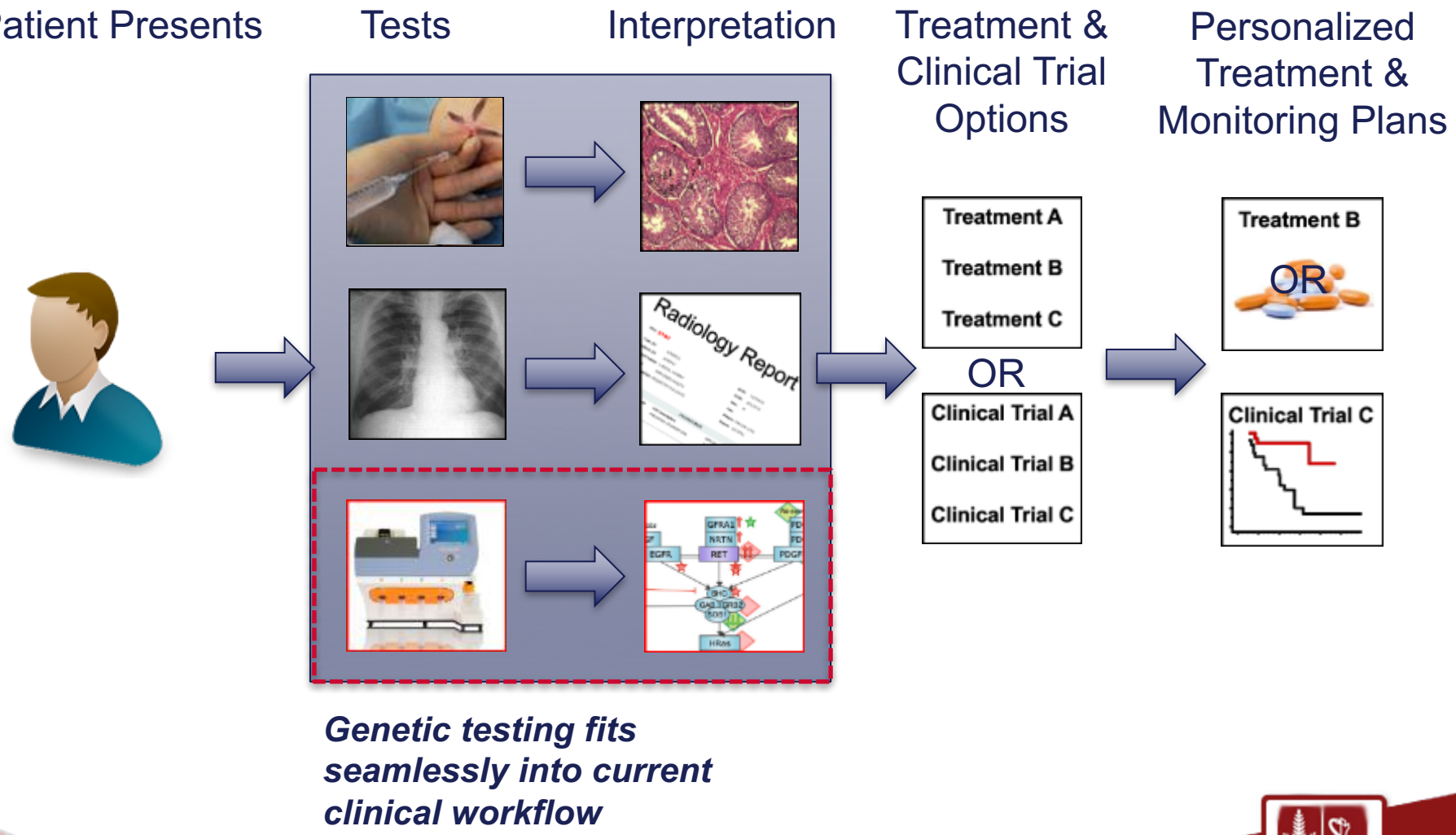
From Bench to Bedside: New Clinical Workflow



Genetic testing fits seamlessly into current clinical workflow