

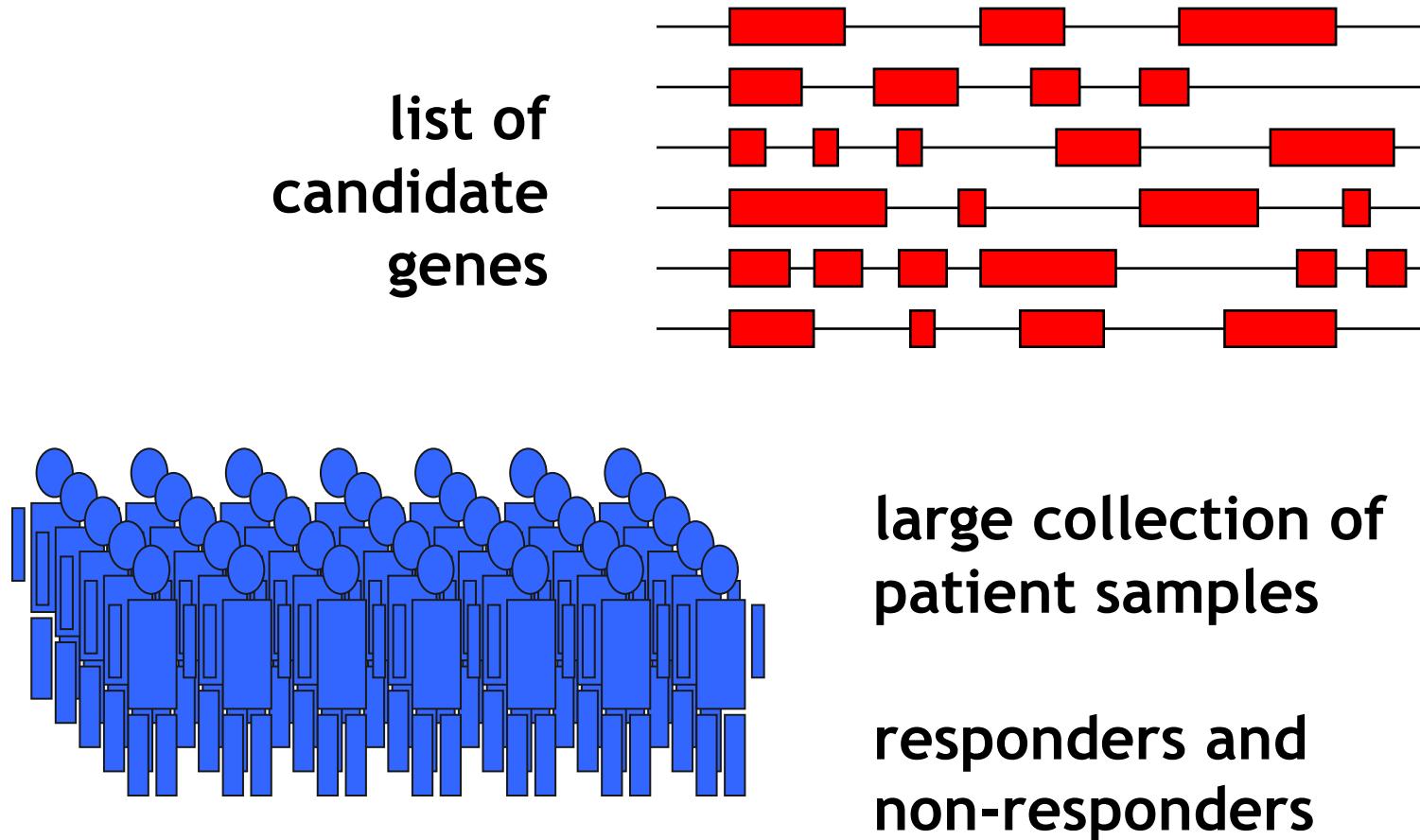
Genomic Medicine & Course wrap-up

BFX-Workshop
Applied Bioinformatics for Genomics
Chris Miller, Ph.D.

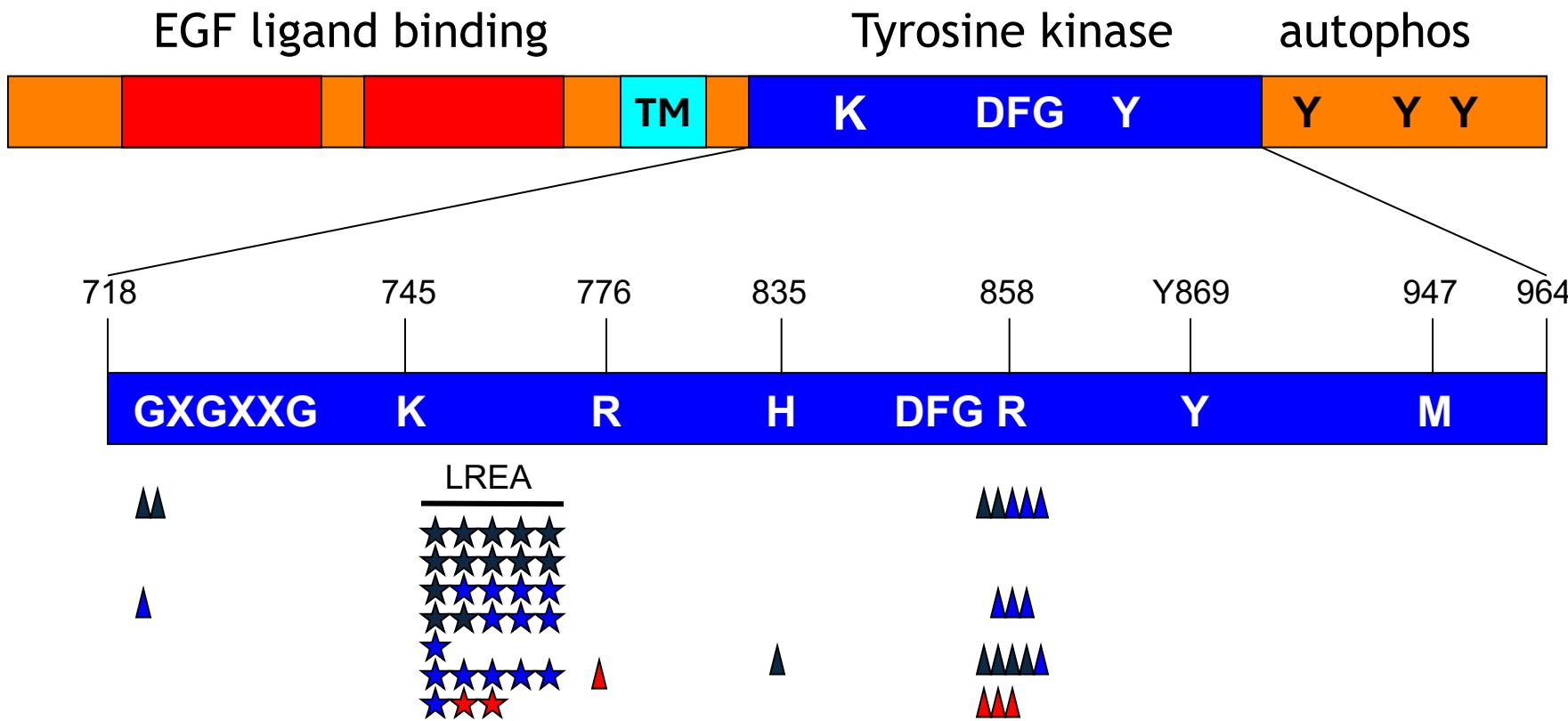
Pre-genomics cancer treatment

- Try Drug A
- If they don't respond, try Drug B
- If they don't respond, try Drug C
- ...

Targeted sequencing



EGFR mutations in never-smoker lung cancer



~80% of Iressa responders have EGFR mutations



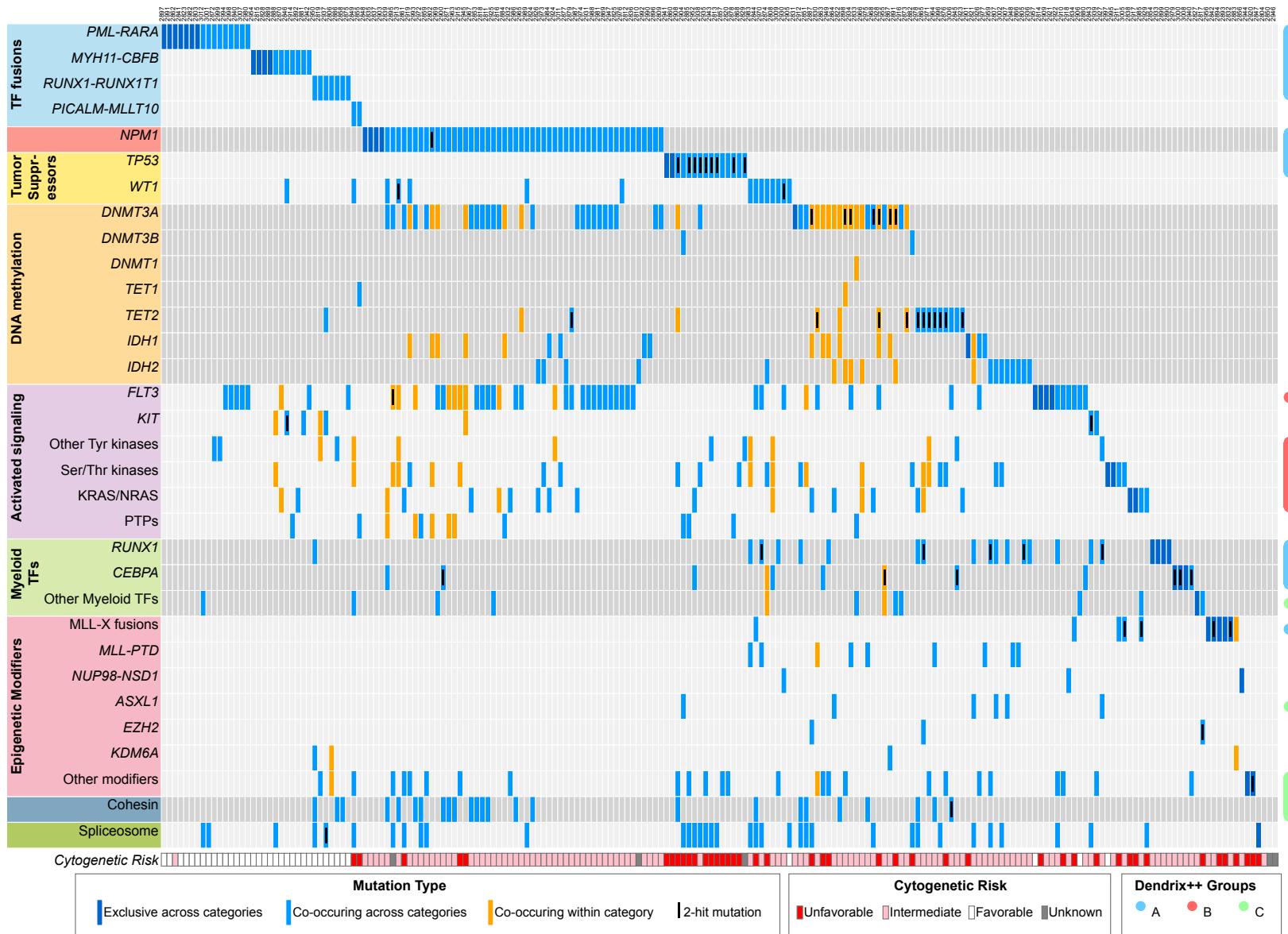
Personalized Genomic Medicine

- Using genomic tests to choose the right treatment for the right patient at the right time

Personalized Genomic Medicine

- Using genomic tests to choose the right treatment for the right patient at the right time
- Cancer is not one disease!

Recurrent somatic mutations in 200 AML patients



TCGA Network, NEJM 2013

Lots of other poorly-defined diseases

- Multiple originating mutations giving rise to similar phenotypes
 - Cancer
 - Autosomal recessive deafness
 - Irritable bowel syndrome
 - many neurodevelopmental disorders
-

Lots of other poorly-defined diseases

- Multiple originating mutations giving rise to similar phenotypes
 - Cancer
 - Autosomal recessive deafness
 - Irritable bowel syndrome
 - many neurodevelopmental disorders
- Complex diseases with both environmental and genetic causes
 - Heart disease, diabetes, etc
 - Doses/metabolism
-

Lots of other poorly-defined diseases

- Multiple originating mutations giving rise to similar phenotypes
 - Cancer
 - Autosomal recessive deafness
 - Irritable bowel syndrome
 - many neurodevelopmental disorders
- Complex diseases with both environmental and genetic causes
 - Heart disease, diabetes, etc
 - Doses/metabolism
- Treatments often work for only a small portion of the disease population

Genomic Medicine?

**FDA Approves First Gene Therapies to Treat
Patients with Sickle Cell Disease**

**Trikafta safe, effective for treating
CF in analysis of clinical trials**

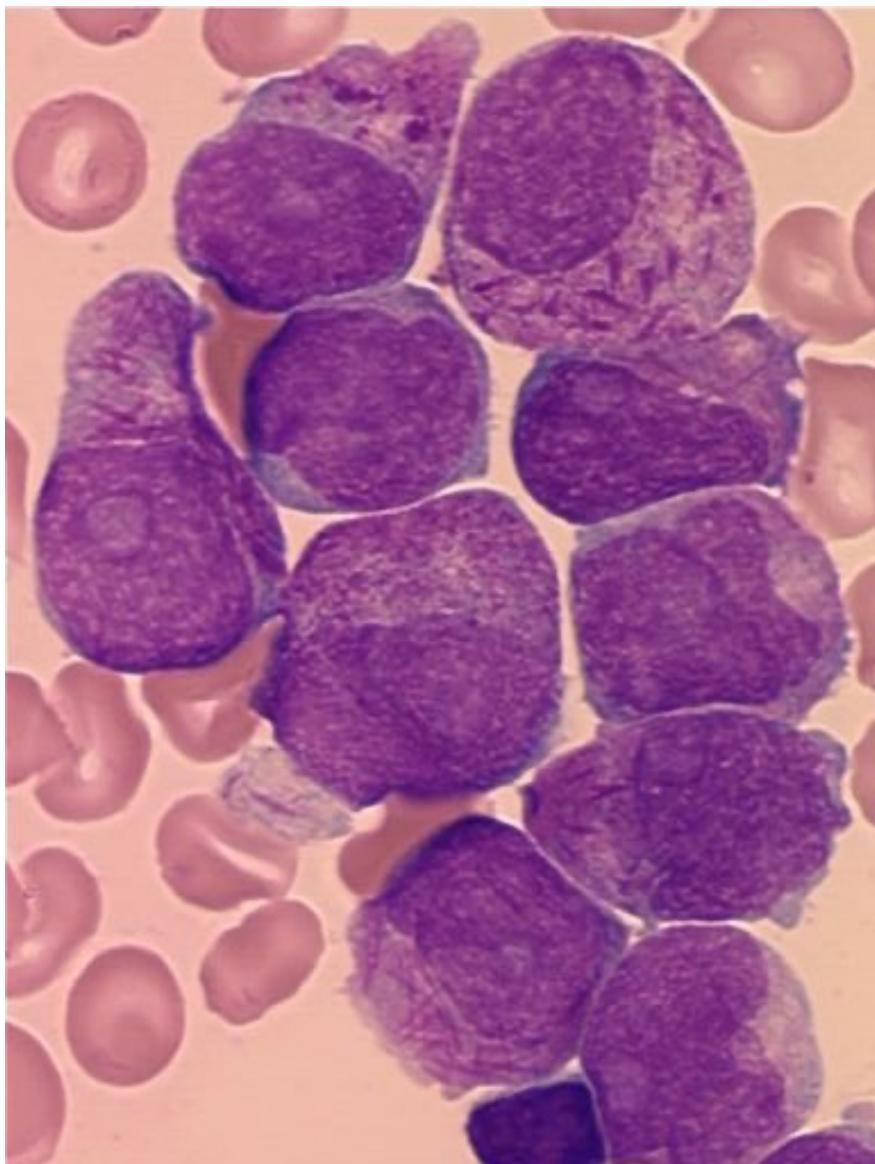
Researchers compared therapy against 2 other CFTR modulators, placebo

**Gene Therapy Shows Promise in Initial
Trial for Patients with Childhood
Blindness**

Penn Medicine researchers delivered working copies of the gene GUCY2D to the eyes of patients with severe vision impairments

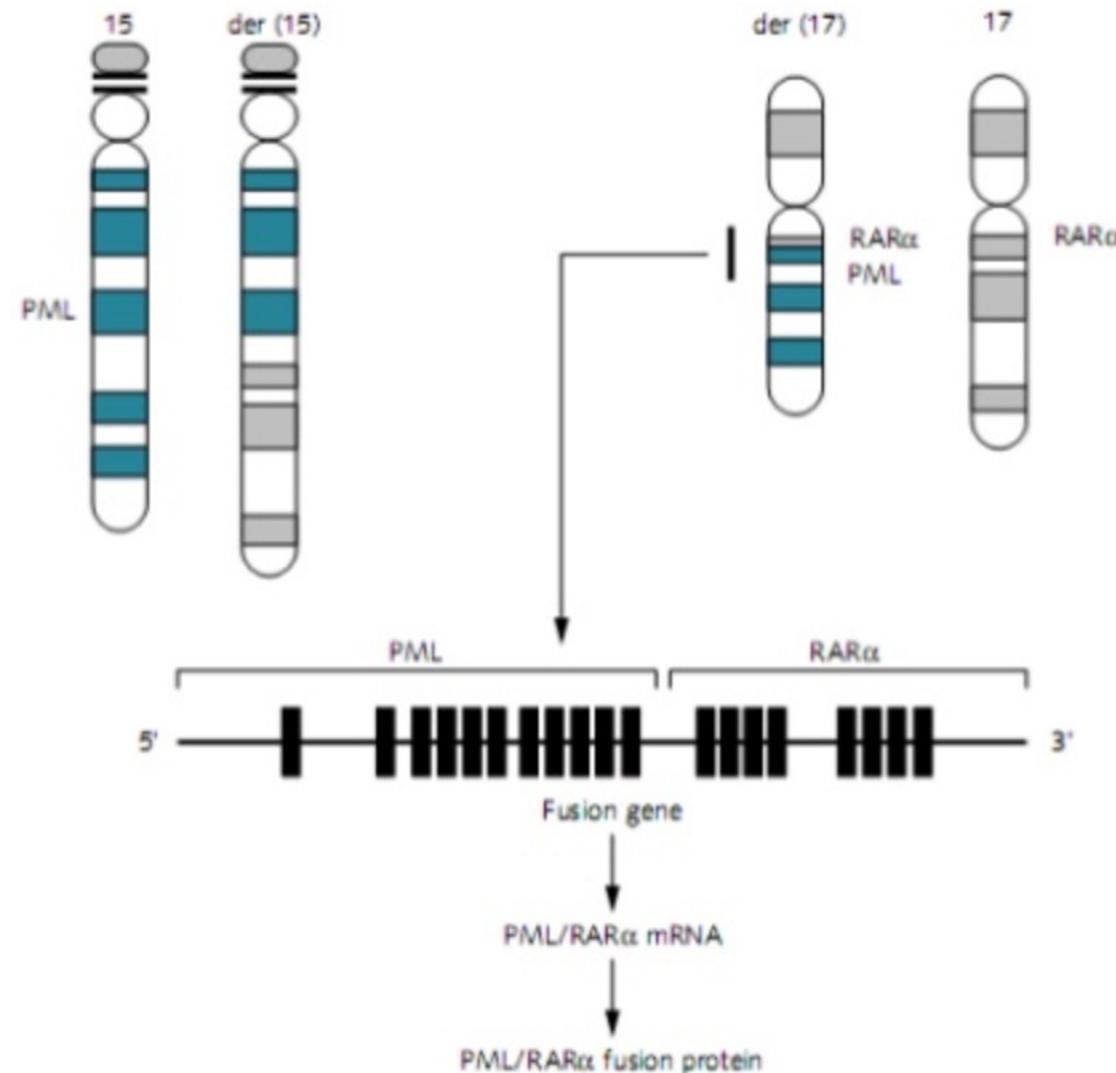
Certainly genomics played a role!

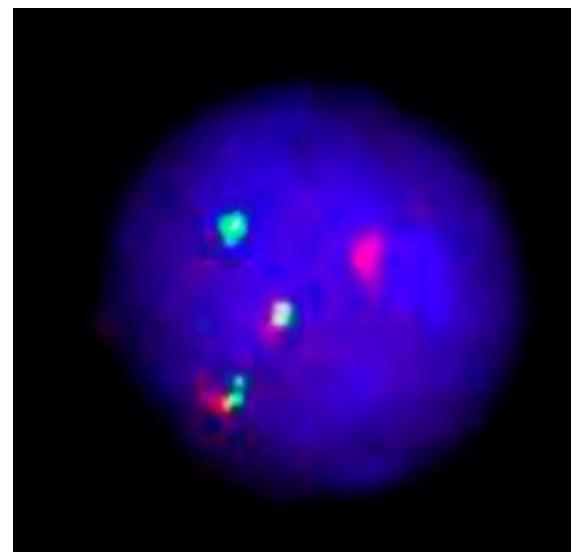
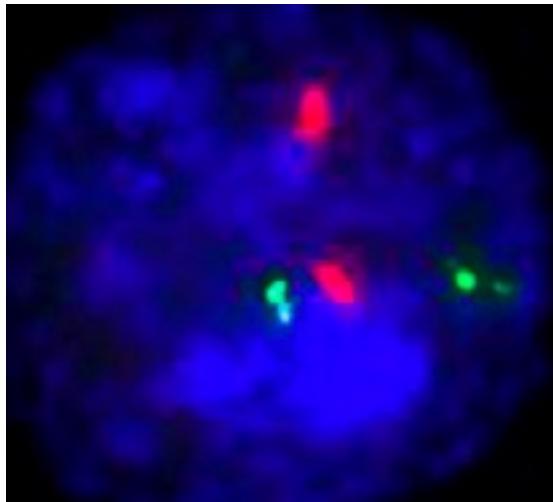
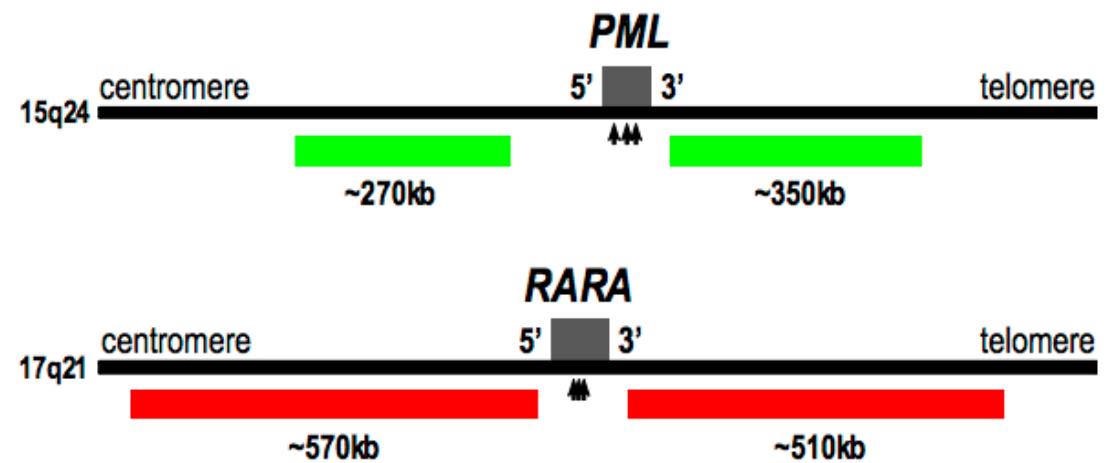
AML52: An atypical M3 AML



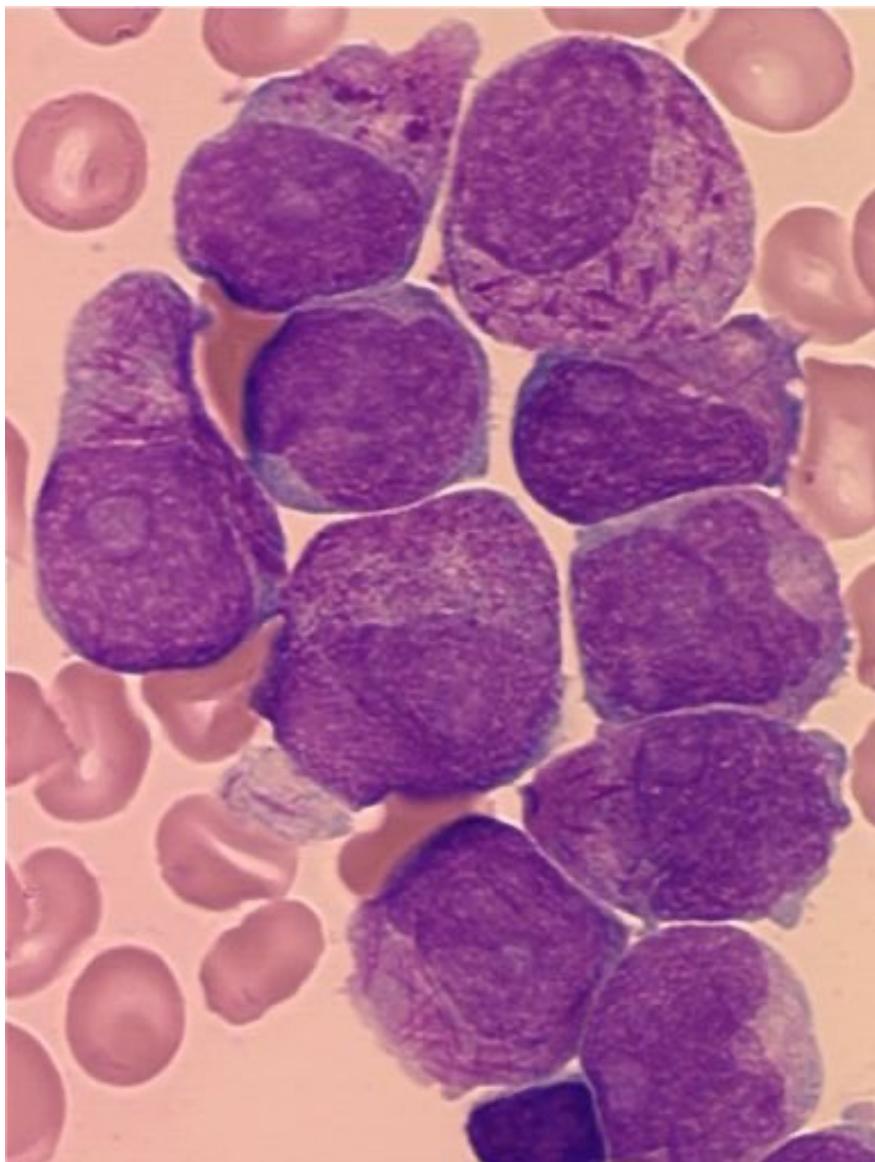
37 y.o. female with AML;
M3 morphology

PML-RARA fusion





AML52: An atypical M3 AML



37 y.o. female with AML;
M3 morphology

Chemo + ATRA

Complex cytogenetics,
negative for PML-RARA

Chemo only

Achieved remission, but faced decision
Referred to WUSTL

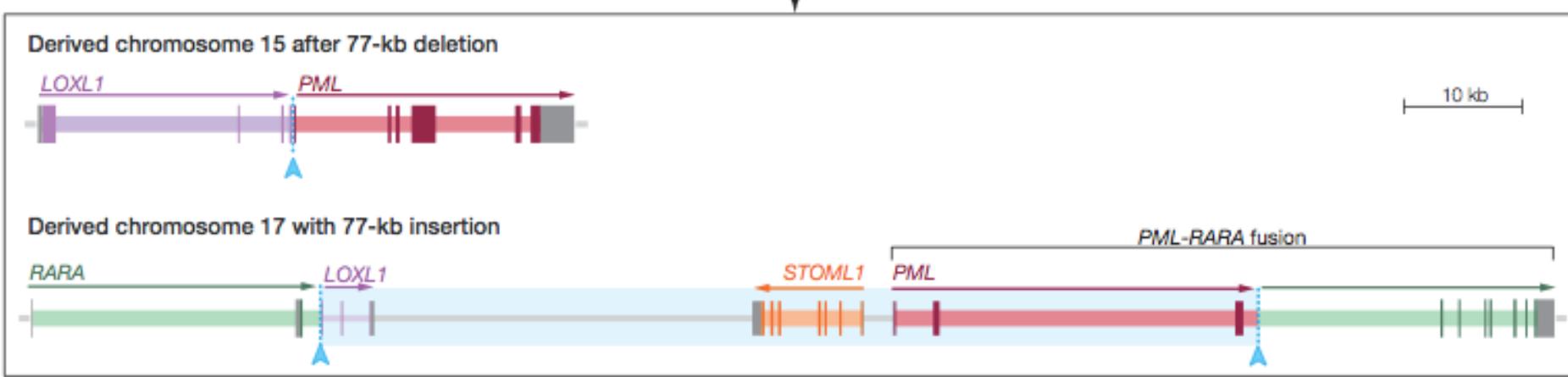
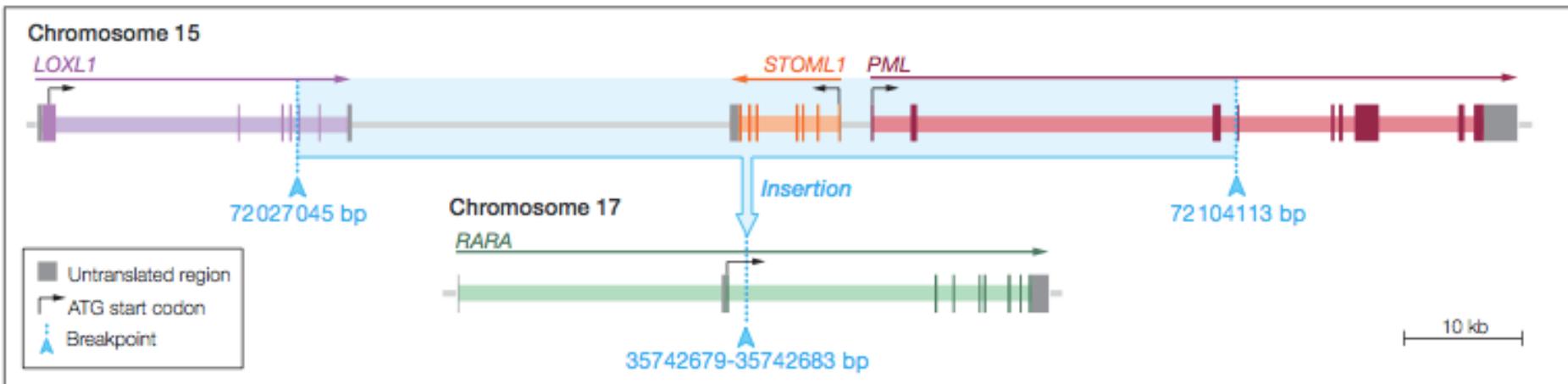
???

Allogeneic
SCT

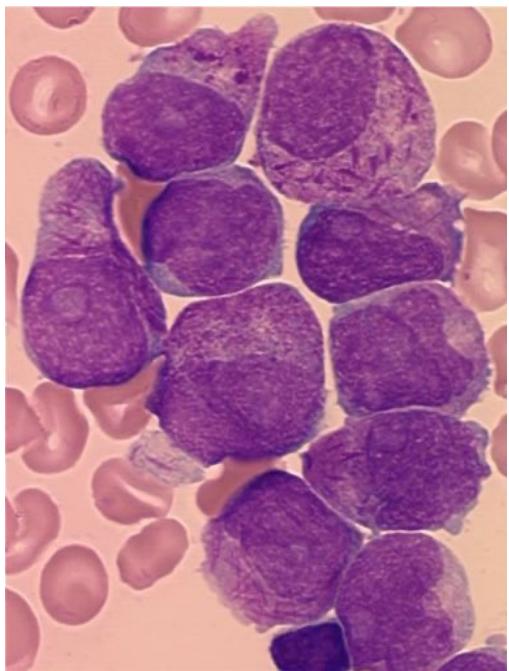
Consolidation
+ ATRA

Use of Whole-Genome Sequencing to Diagnose a Cryptic Fusion Oncogene

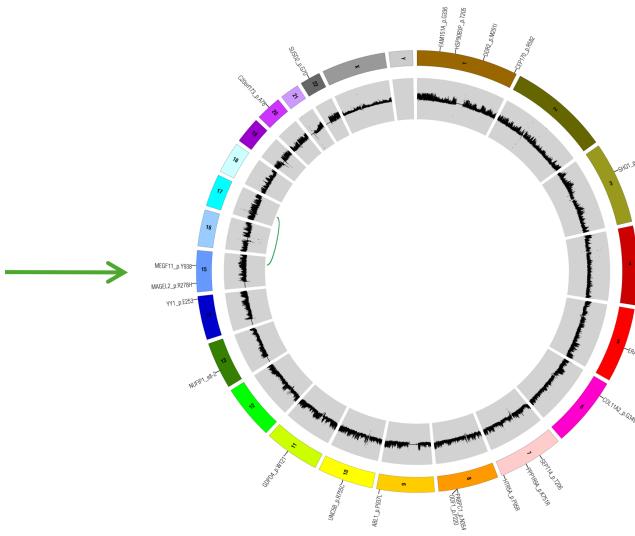
A Breakpoints in chromosomes 15 and 17 resulting in *PML-RARA* fusion



AML52: An atypical M3 AML



37 y.o. female with
de novo AML,
M3 morphology,
CTG, no PML-
RARA.
Referred to WUSM
for SCT.

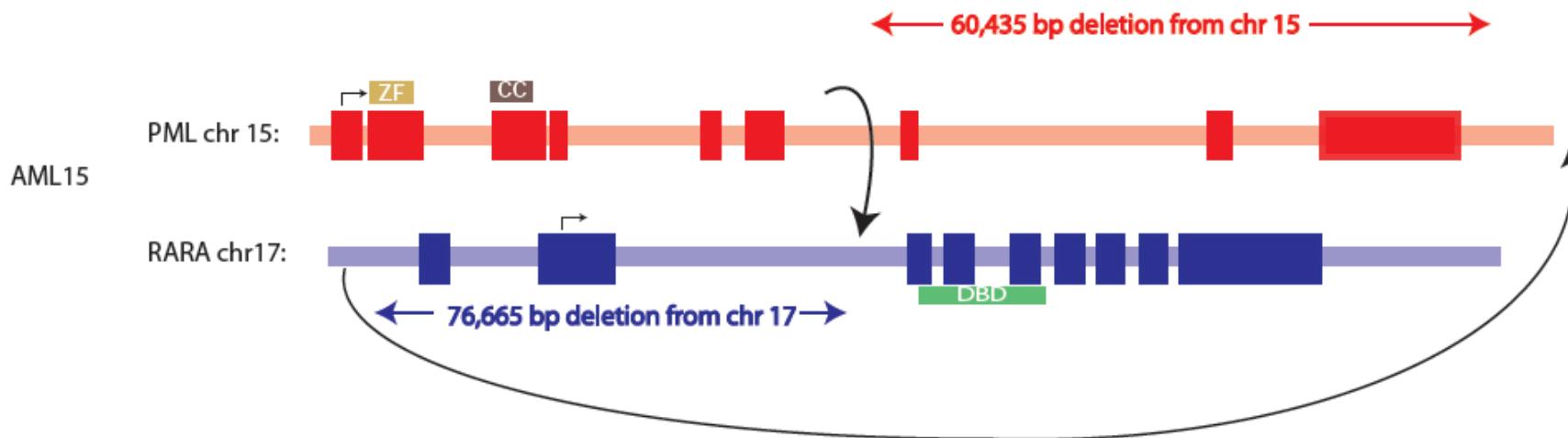
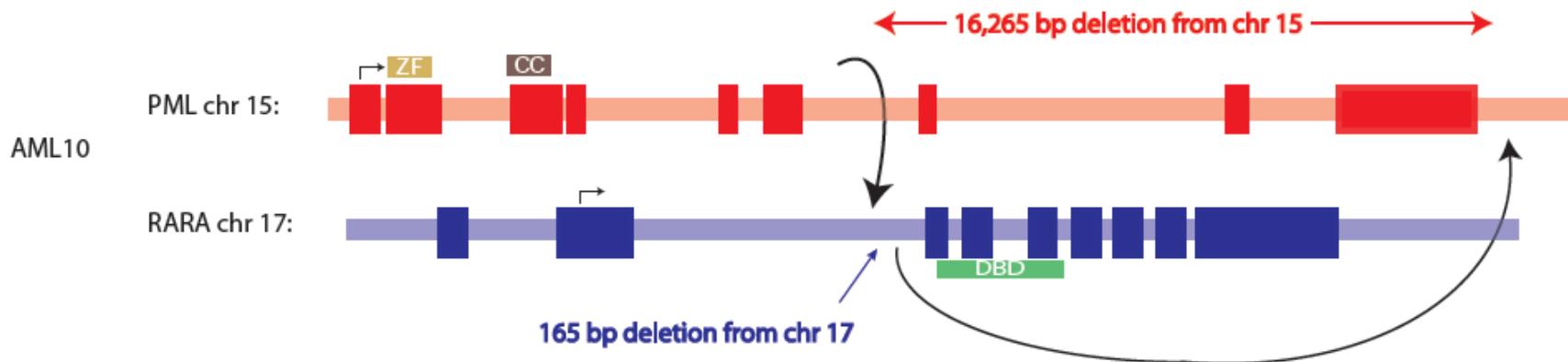


Detection of
PML-RARA
fusion by WGS.
Confirmed by
FISH, RT-PCR

Consolidation:
Chemo + ATRA

Sustained remission

Additional cryptic M3 AMLs



The New York Times

In Treatment for Leukemia, Glimpses of the Future



► Second Chance: Lukas Wartman, a leukemia doctor and researcher, developed the disease himself. As he faced death, his colleagues sequenced his cancer genome. The result was a totally unexpected treatment.

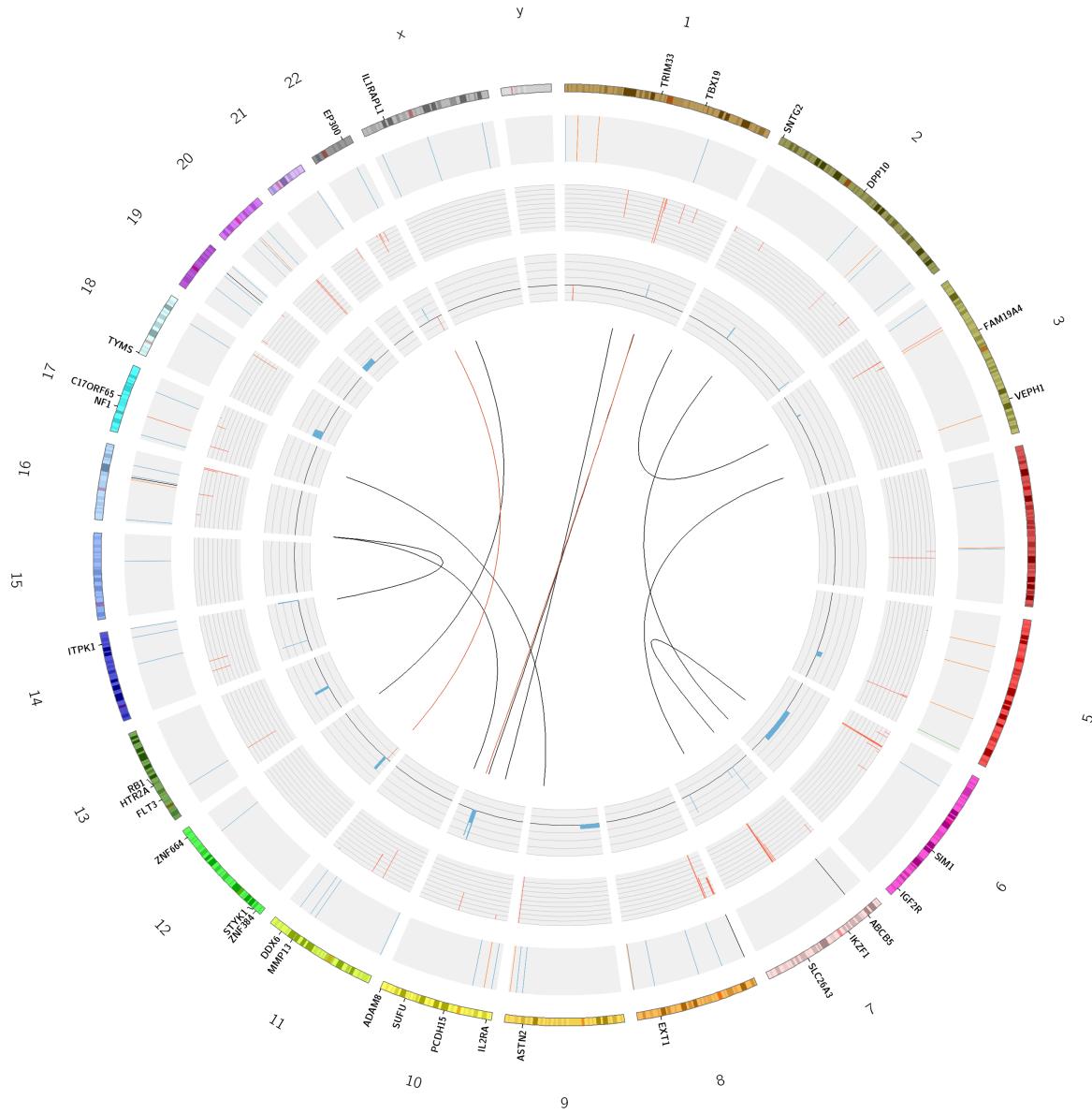
By **GINA KOLATA**

Published: July 7, 2012

A case study in personalized medicine

- Diagnosed with acute lymphocytic leukemia (B-ALL) - age 25
 - chemotherapy, achieved remission
- Relapse - age 30,
 - salvage chemo to remission; Stem cell transplant
- Severe 2nd relapse in July 2011 - age 33
 - CNS involvement.
- Whole genome, exome and RNA sequencing
 - initiated on August 1, 2011,
 - completed by early Sept 2011.

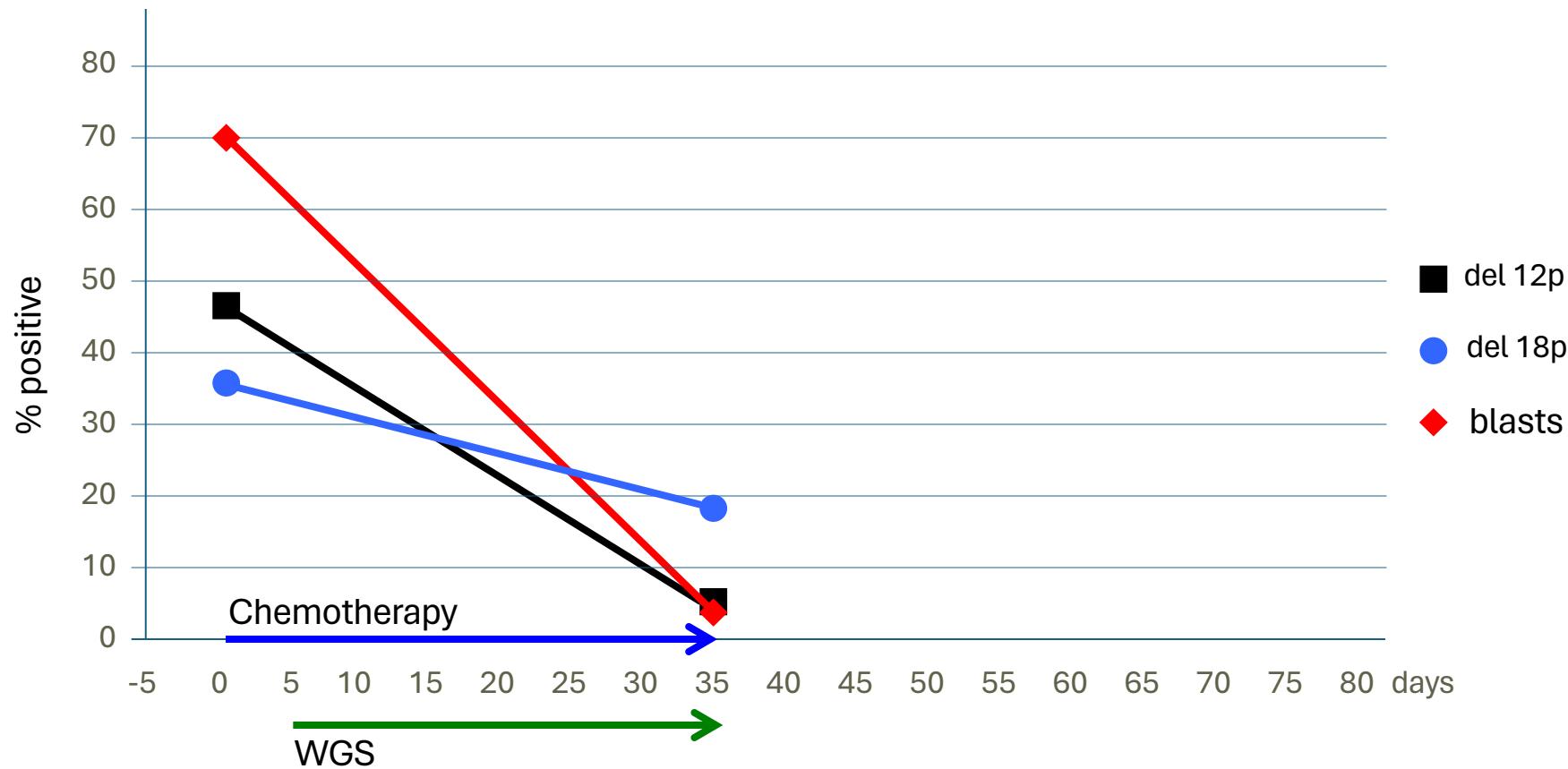
ALL1 genome summary (WGS/Exome/RNA-Seq)



Notable mutations

- *EP300*
- *NF1*
- *EXT1*
- *DDX6*
- *IL2RA*
- *MMP13*

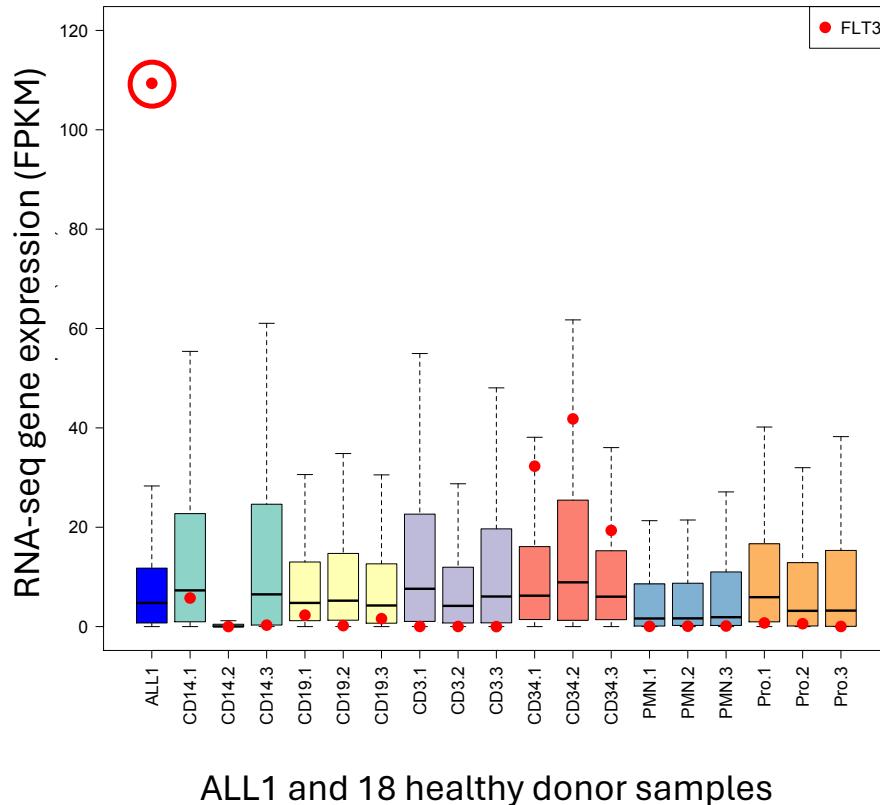
FISH at apparent remission



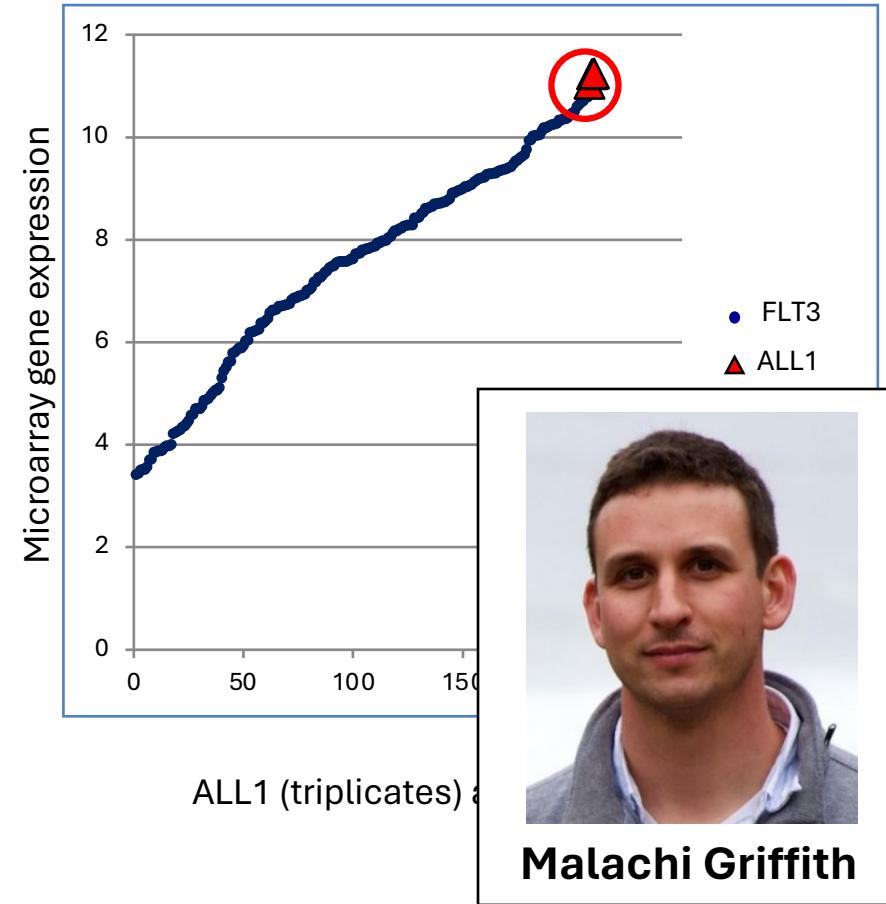
- By conventional pathology, the patient appeared to be in remission following salvage chemotherapy.
- The more highly sensitive i-FISH analysis indicated presence of treatment refractory disease. Hence, the patient was unable to receive transplant.

Extreme *FLT3* over-expression

RNA-seq expression data

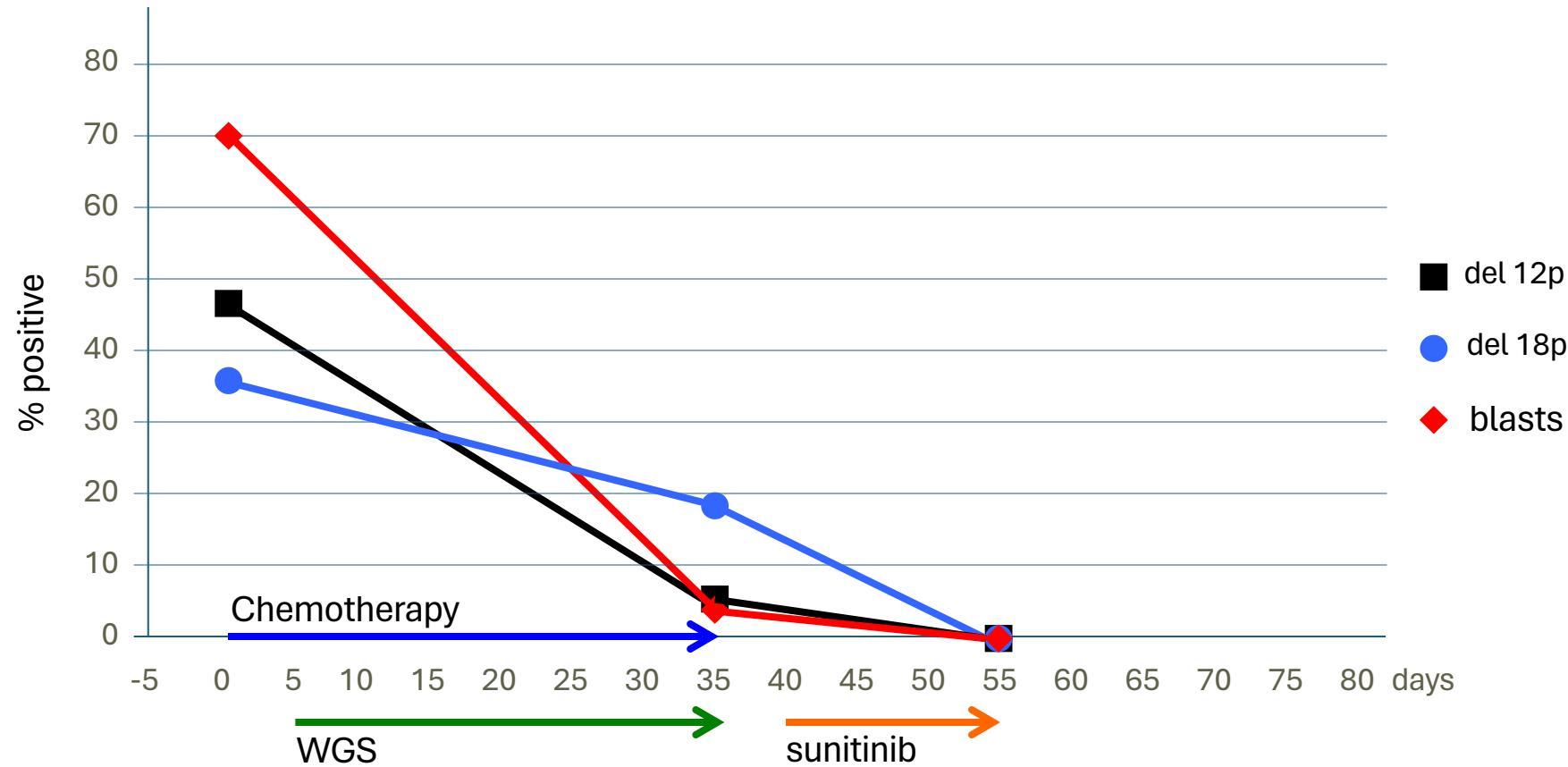


Microarray expression data



★ Targeted therapeutic for activated *FLT3*: sunitinib

FISH after targeted therapy



- No tumor cells detected following a 12-day course of sunitinib.
- Patient was able to receive a transplant to complete his treatment.

A case study in personalized medicine

- Sunitinib created a complete clinical remission in 12 days, enabling SCT (September 28, 2011).
- Genomic markers provided therapeutic options and better detection of residual disease
- Today: more than thirteen years post-SCT, Dr. Wartman is still alive!



Treatment is still tough

A stem cell transplant helped beat back a young doctor's cancer. Now, it's assaulting his body

A few months before completing medical school in 2003, Lukas Wartman was diagnosed with acute lymphoblastic leukemia (ALL), a blood cancer that's particularly lethal when it strikes adults. So began a battle to stay alive that has involved more than 70 drugs, two rounds of cell transplants, and a staggering series of twists and turns.

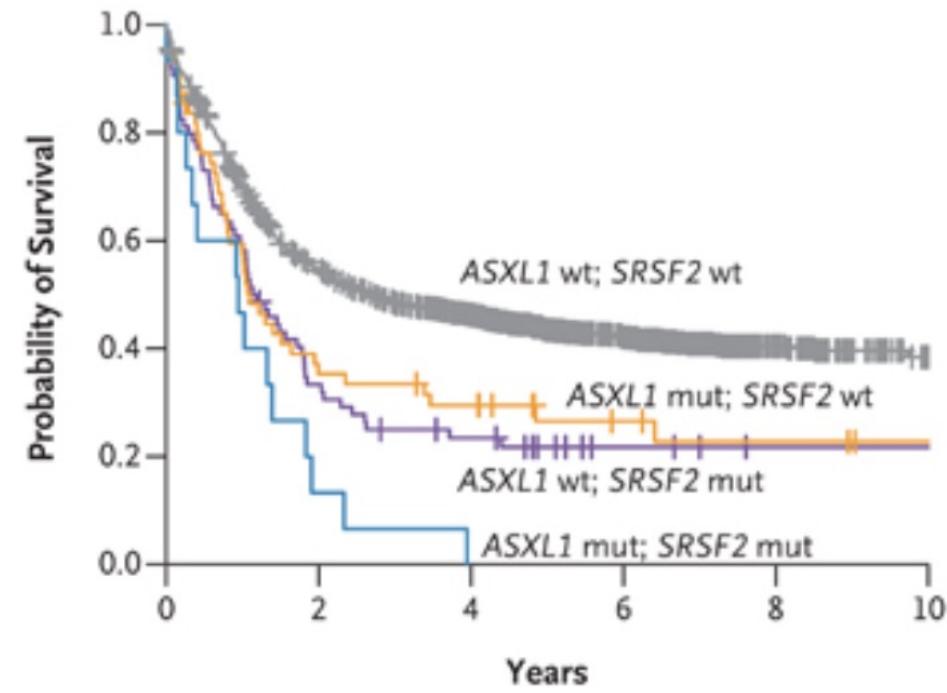
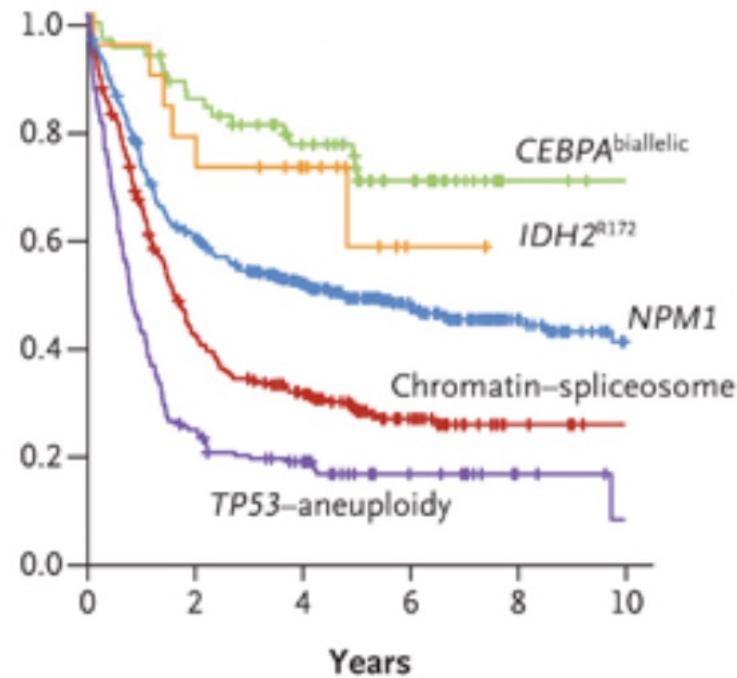
Wartman immediately received aggressive chemotherapy, which drove the cancer into remission and enabled

Lukas Wartman from Washington



Still work to do

- Genomic medicine is here



- Too often, no treatment options

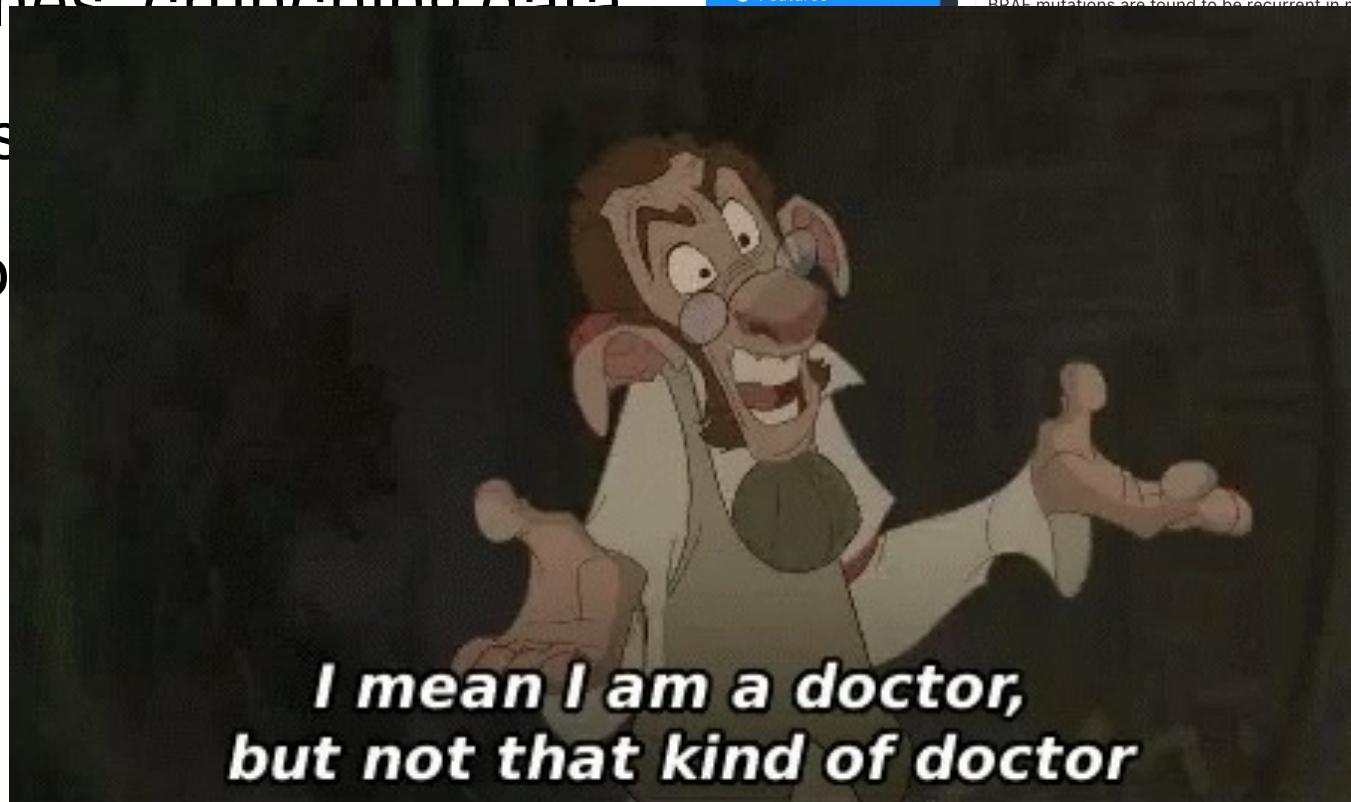
Still work to do

- Genomic medicine requires expertise in bioinformatics
- Building pipelines, crunching data
- Interpreting results
- Curating databases

The screenshot shows the CIViC website interface for the BRAF gene. The left sidebar has a dark background with white text and icons, listing categories like Assertions, Evidence, Molecular Profiles, Features (which is selected and highlighted in blue), Variants, Variant Groups, Clinical Trials, Diseases, Therapies, Phenotypes, Sources, Variant Types, Curation, Activity, and Queues. The main content area has a light background. At the top, there's a search bar, navigation links for Home, About CIViC, Help, Documentation, and Sign In / Sign Up. Below that, the URL is 'Features / BRAF / Summary'. The main content includes a 'Description' section with text about BRAF mutations being recurrent in many cancer types, with V600E being the most prevalent activating mutation. It also lists 'Sources' (PubMed articles from 2009, 2013, and 2017), 'Aliases' (B-RAF1, B-raf, BRAF1, NS7, RAFB1), and 'Resources' (DGIdb, ProteinPaint). To the right, there's a 'MyGeneInfo' sidebar with tabs for Overview (which is selected), Summary, and Protein Domains. It shows Entrez Symbol: BRAF (ID: 673), UniProtKB ID: P15056, Chromosome: 7, Strand: -1, Start: 140419127, Stop: 140624564, and a table with rows for Aliases, Protein Domains, and Pathways. At the bottom, there are tabs for Molecular Profiles and Variants, and a section for Data Releases.

Still work to do

- Genomic medicine requires expertise in bioinformatics
- Building pipelines, crunching data
- Interpreting results
- Curating databases



Screenshot of the CIViC (Clinical Interpretation of Variants in Cancer) website showing the BRAF gene summary page.

The main header includes the CIViC logo, a search bar, and navigation links for Home, About CIViC, Help, Documentation, and Sign In / Sign Up.

The left sidebar, titled "KNOWLEDGEBASE", contains links for Assertions, Evidence, Molecular Profiles, and Features (which is currently selected).

The main content area displays the "GENE BRAF" page. It includes a "Summary" tab and other tabs for Comments, Revisions (with 2 notifications), Flags, and Events. It also shows "Curators" and "Editors".

The "Description" section states: "BRAF mutations are found to be recurrent in many cancer types." Below this, there is a "Description" section with a "Summary" tab and other tabs for Comments, Revisions (with 2 notifications), Flags, and Events. It also shows "Curators" and "Editors".

On the right side, there is a "MyGeneInfo" panel with sections for Overview, Summary, and Protein Domains. It provides details about the Entrez Symbol (BRAF ID: 673), UniProtKB ID (P15056), Chromosome (7), Strand (-1), Start (140419127), and Stop (140624564). It also lists Aliases (B-RAF1, B-raf, BRAF1, NS7, RAFB1), Protein Domains (Diacylglycerol/phorbol-ester binding, Protein kinase C-like, phorbol ester/diacylglycerol acyltransferase), and Pathways (Downstream signaling in naïve CD8+ T cells, CDC42 signaling events, ErbB1).

Course Review

- Bioinformatics is a journey, not a destination



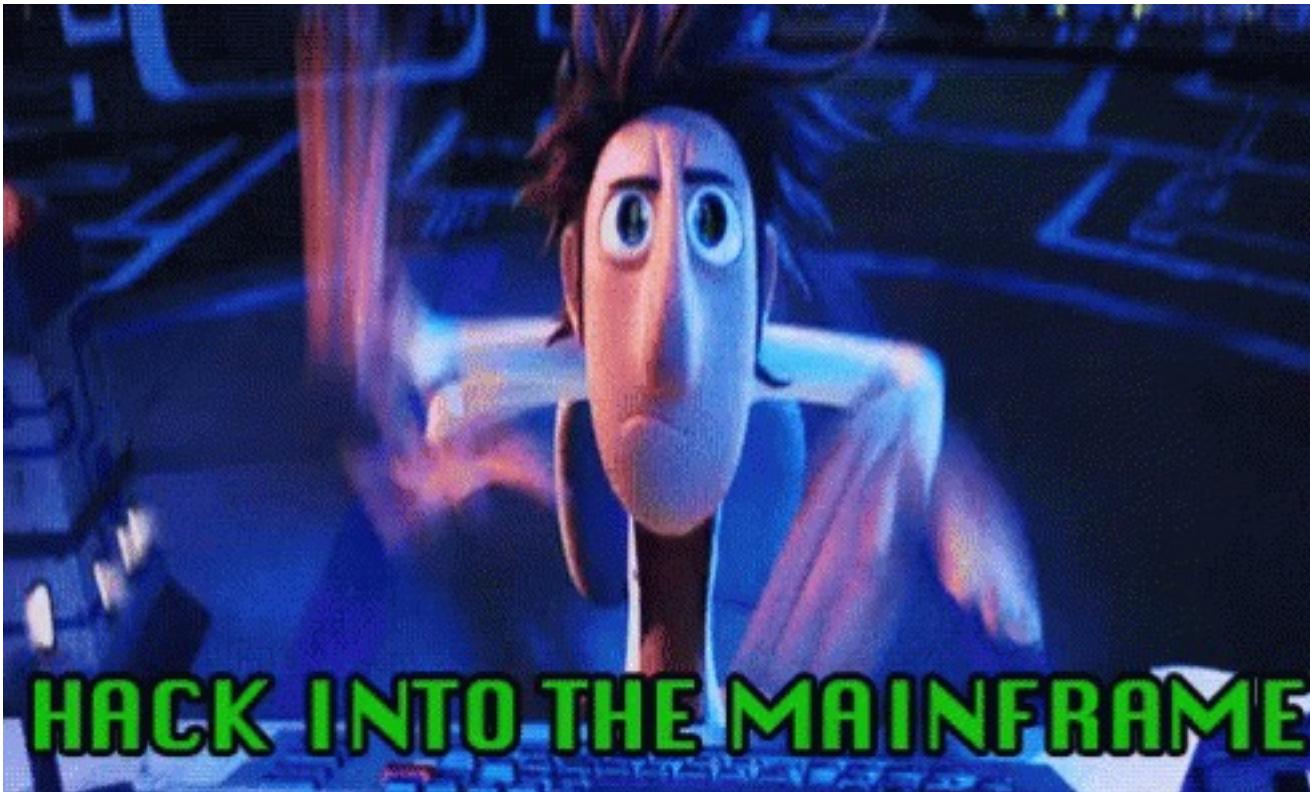
Course Review

- Shallow but broad, instead of deep and focused



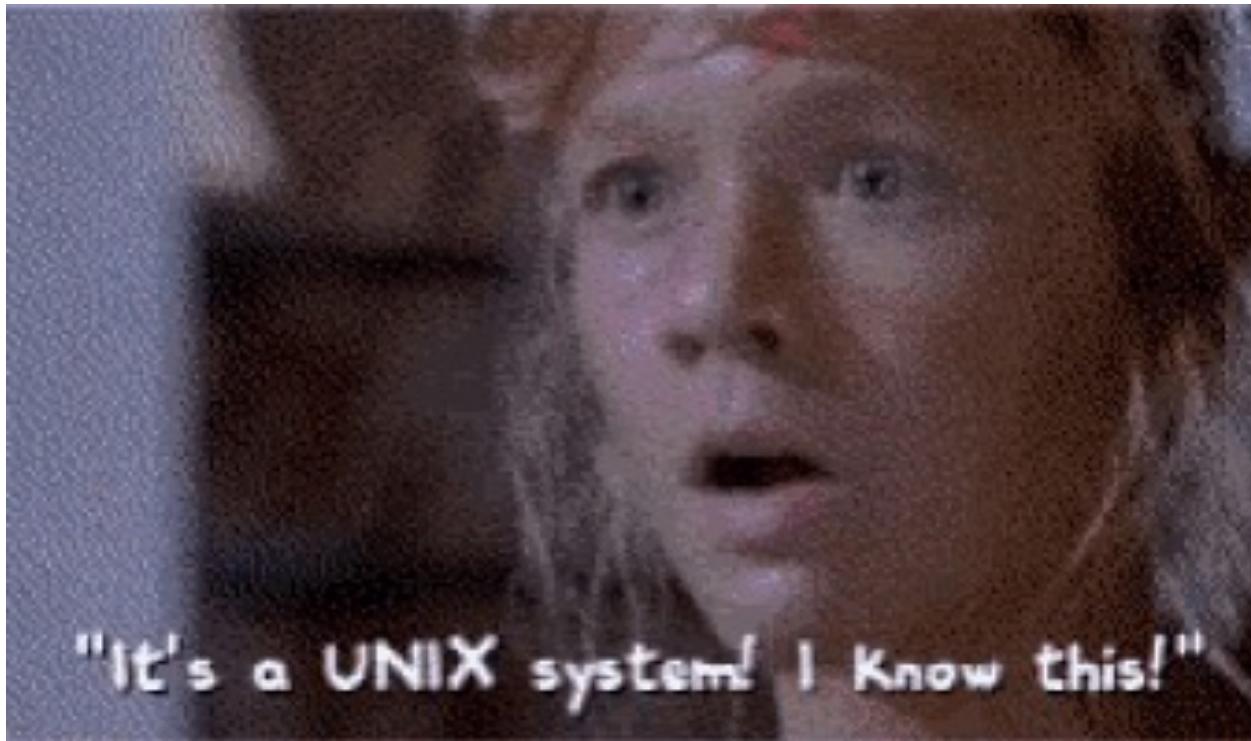
Course Review

- The goal wasn't to turn everyone into computational experts



Course Review

- Give you familiarity with tools, conventions, and data types



"It's a UNIX system! I know this!"

Foundational skills

- Command line skills
- How to install packages in R or python
- How to find and use a docker container with the tools you need

```
acer@acer-PC MINGW64 ~/Desktop/New folder/Code
$ chmod +x shellscripts/demo.sh

acer@acer-PC MINGW64 ~/Desktop/New folder/Code
$ ./shellscripts/demo.sh
Hello from BASH
A very basic script
This is some text echoed

acer@acer-PC MINGW64 ~/Desktop/New folder/Code
$ ./demo.sh
bash: ./demo.sh: No such file or directory

acer@acer-PC MINGW64 ~/Desktop/New folder/Code
$
```



Foundational skills

- How to run things in different computing environments



Laptop



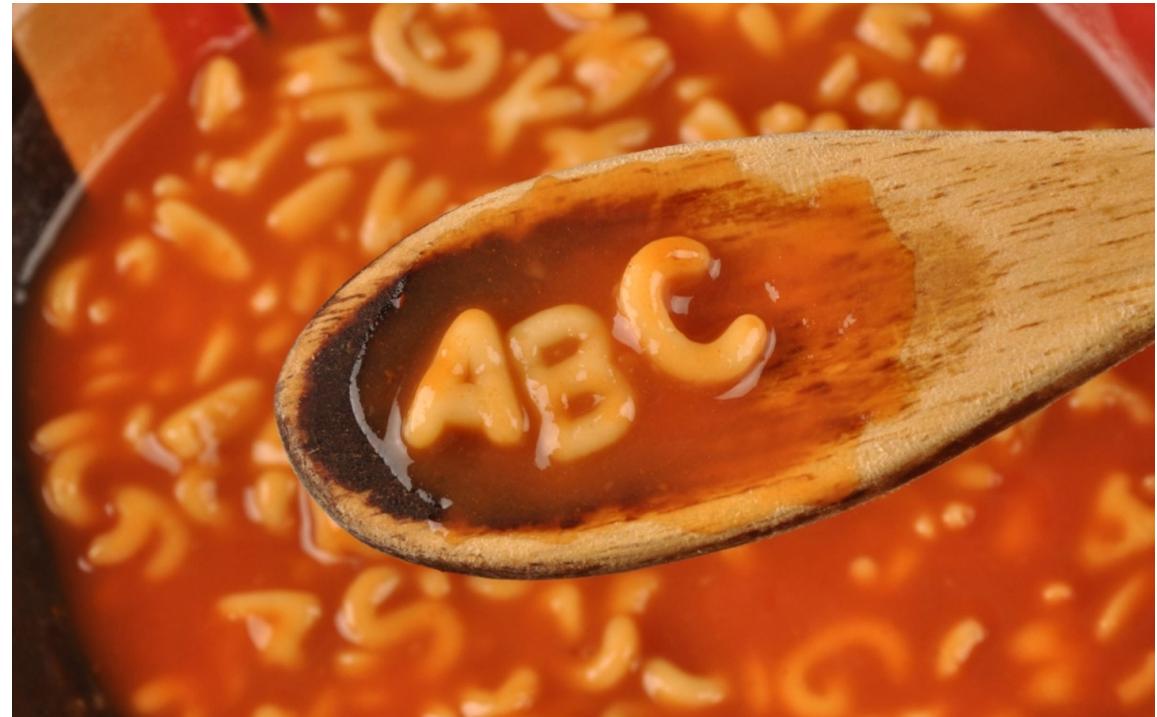
Cluster



Cloud

Foundational skills

- Understanding raw data formats and files
 - FASTQ, BAM, CRAM, BED, GTF, VCF



A place to start

- An idea of first steps to take with your data
- QC, Alignment, feeding into workflows



Foundational skills

- Exposure to different tools and techniques that you can apply
- "This looks like a problem that we can answer with scRNA-seq!"

Foundational skills

- Exposure to different tools and techniques that you can apply
 - "This looks like a problem that we can answer with scRNA-seq!"
 - "This is **not** a problem that we can answer with scRNA-seq!"

Foundational skills

- Ideas of what happens when something goes wrong
 - Interpreting error messages
 - Troubleshooting experimental data
 - Using controls in your computational experiments

Foundational skills

- Ideas of what happens when something goes wrong
 - Interpreting error messages
 - Troubleshooting experimental data
 - Using controls in your computational workflows
- Don't trust your data until you have no other choice!

Thanks

- Jason Walker
- Susanna Kiwala
- Kartik Singhal
- My Hoang
- Mariam Khanfar
- Jennifer Foltz
- Juan Macias
- Brigida Rusconi
- Malachi Griffith
- Jenny McKenzie
- John Garza



Institute of Clinical and
Translational Sciences

Supported by CTSA Grant
UL1 TR002345