ESMO SARCOMA & GIST

An ESMO Meeting

WHAT IS THE STATUS OF SARCOMA RESEARCH SO FAR AND WHAT NEEDS TO BE CHANGED IN THE FUTURE FROM AN EXPERT PERSPECTIVE?

Sarcoma Patients EuroNet

Robert Maki, MD PhD
University of Pennsylvania Perelman School of Medicine
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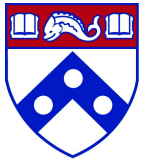
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



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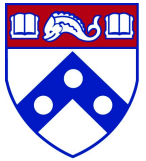

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Disclosure slide

Consulting fees, honoraria

- AADi
- Bayer
- Deciphera
- Janssen / Pharma Mar
- Karyopharm
- Presage
- Sarcoma Alliance for Research through Collaboration (SARC)
- Springworks
- ASCO
- ESMO
- UptoDate

Clinical trials support to institution

- Bayer
- Karyopharm
- Springworks
- Presage
- Sarcoma Alliance for Research through Collaboration (SARC)

Outline

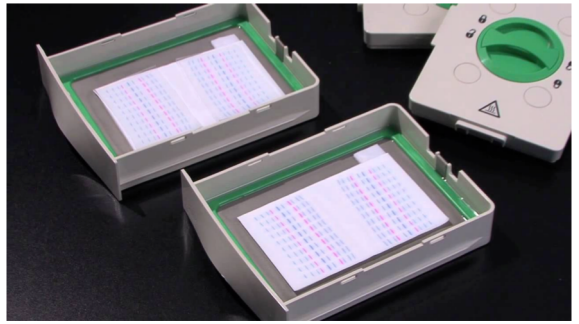
- Definition of research
- Examples of research
- Determinants of progress in research
- Areas of greatest change in sarcoma research
- What's wrong, and what can be done?

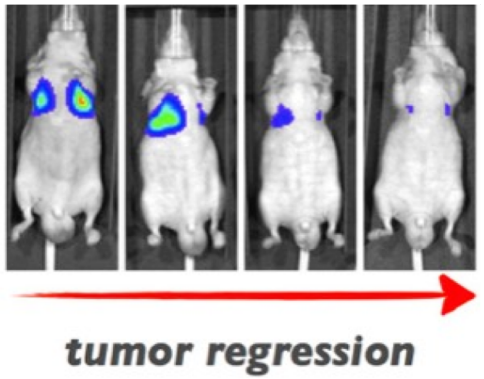
Definition of Research

- Merriam-Webster
  - Careful or diligent search
  - Studious inquiry or examination
  - The collecting of information about a particular subject
- OED
  - Systematic investigation or inquiry aimed at contributing to knowledge of a theory, topic, etc. by careful consideration, observation of study of a subject

Sarcoma Research: some items overlap or are concurrent

- Basic Science
  - Wet lab
    - Cell lines or primary tumor tissues
    - Whole cells or constituent components
  - Dry lab
    - Modeling, often bio-informatically
    - Programming tools
- Translational
  - Animal models: genetic models, natural models, xenografts
  - Tumor or other sample based
- Clinical
  - Trials
    - Active treatment
    - Supportive care
    - Outcomes
  - Epidemiology, clinical genetics
  - Policy

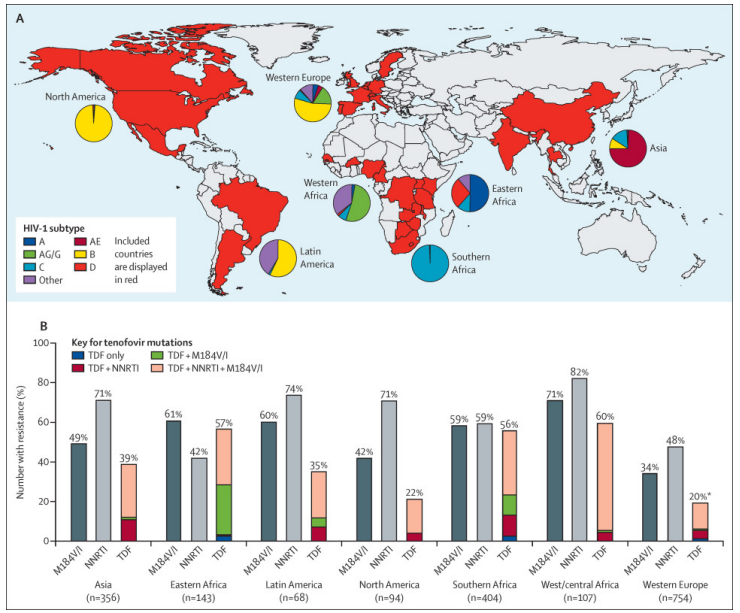




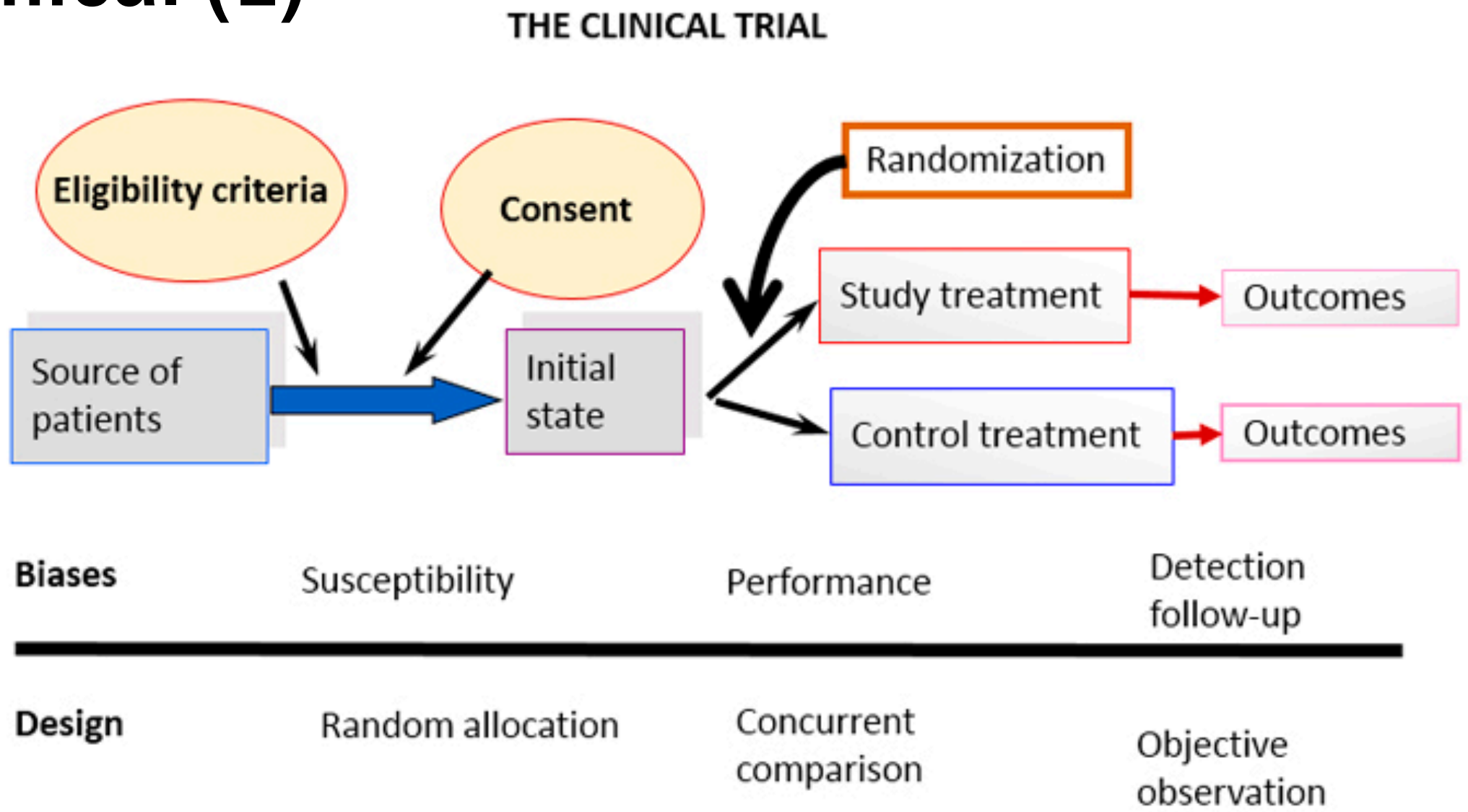
Examples of research topics

Epidemiology, clinical genetics, policy

- Epidemiology
  - How many people have sarcoma in a specific country or region?
  - Are there links to exposures one can identify
  - Is there a way to intervene to minimize the exposure
- Clinical genetics
  - How many people with BRCA syndrome develop sarcomas? Is there any special mutation that is associated with that rare event?
- Policy
  - Should we screen smokers who get sarcoma more carefully for lung metastases or other cancers?
  - What is the cost? What impact did that intervention make?



Clinical (1)


THE CLINICAL TRIAL
Eligibility criteria
Consent
Randomization
Source of patients
Initial state
Study treatment
Outcomes
Control treatment
Outcomes
Biases
Susceptibility
Performance
Detection follow-up
Design
Random allocation
Concurrent comparison
Objective observation

Clinical (1)

vs.

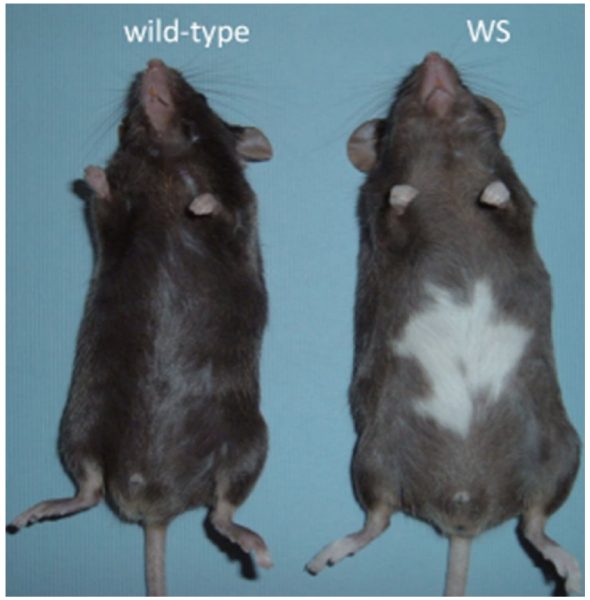
- Is ondansetron needed if you use aprepitant ?
- How do you measure “nausea”?
- How often do you check on patients to see how they are doing?
  - Easier in the age of apps….
- What kind of difference do you expect?
- How many people do you need to show a difference?
- How long will that take?
- How much will it cost?
- Is it really worth doing the study?

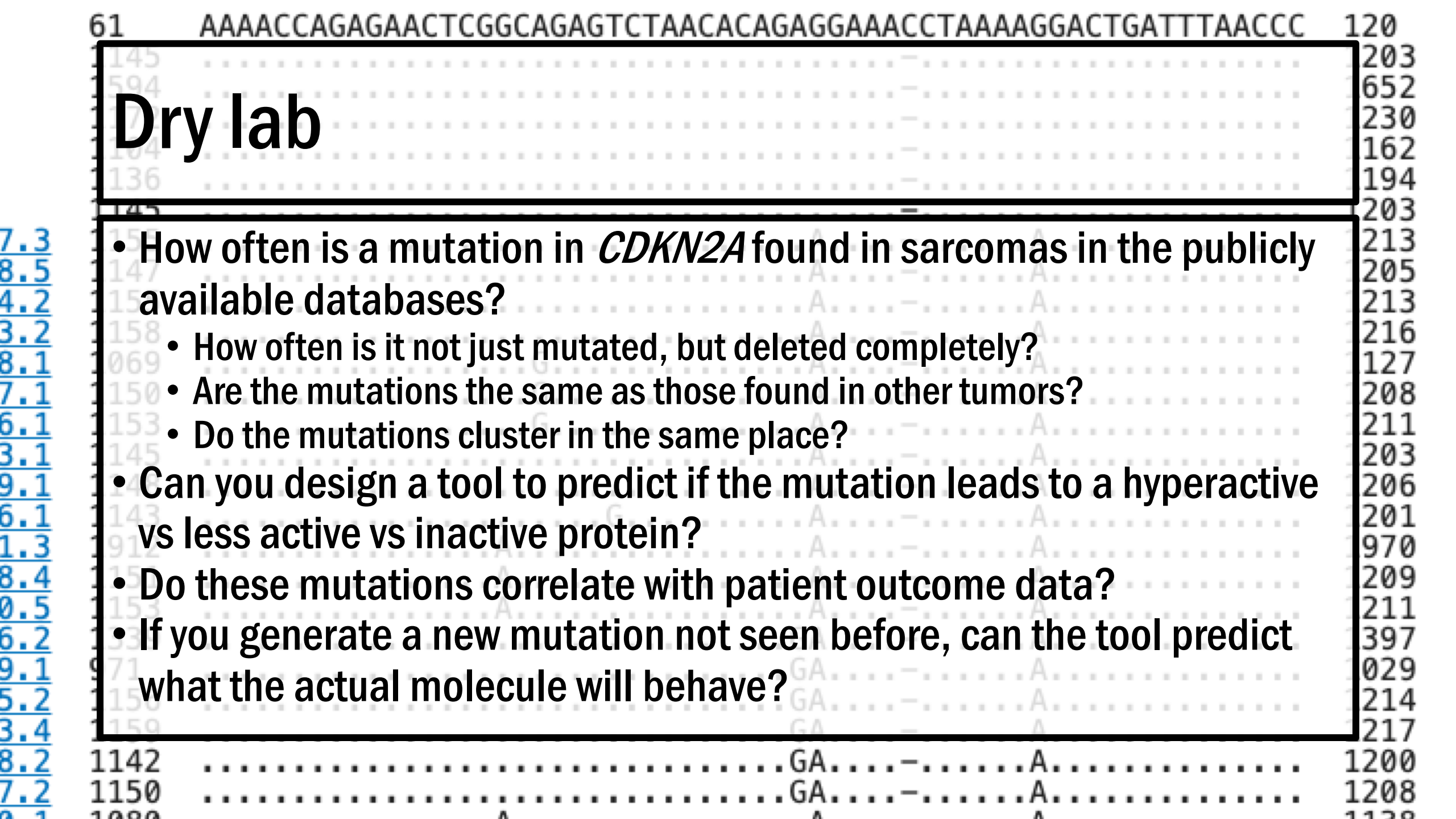
Clinical (2)

- Is doxorubicin and temsirolimus better than doxorubicin alone?
  - Do you have any information that the two drugs might actually do something together?
  - Both cause mouth sores as a bad side effect
- What are the doses of the two drugs that you can use together? (separate study)
- What kind of difference do you expect?
- Will FDA approve the study based on the difference that you expect?
- Do people have to survive longer or just do better as long as they are on treatment?

Wet lab

- Can the mutated receptor KIT, which activates GIST, be found in the nucleus of the cell, and not just at the surface?
  - What is it doing in the nucleus?
  - With which molecules is it associating?
  - Can you delete the KIT molecule only at the cell surface and still find it in the nucleus? Does it act differently?
    - Is it bound to DNA? To other proteins?
    - Does this happen only in GIST cells or does it happen more generally?
    - Can you change the other molecules that KIT sticks to, and if so, how does it change the function?
    - Are there differences between normal cells and cancer cells?

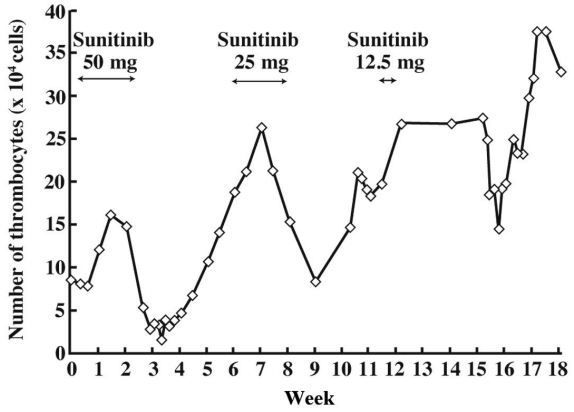




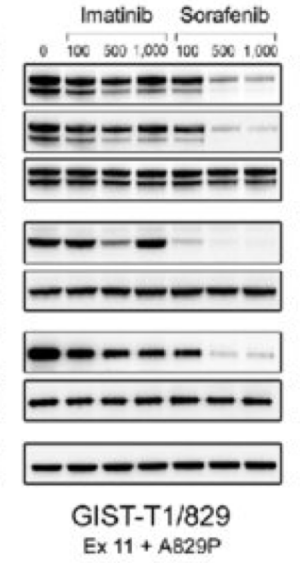
Dry lab

- How often is a mutation in *CDKN2A* found in sarcomas in the publicly available databases?
  - How often is it not just mutated, but deleted completely?
  - Are the mutations the same as those found in other tumors?
  - Do the mutations cluster in the same place?
- Can you design a tool to predict if the mutation leads to a hyperactive vs less active vs inactive protein?
- Do these mutations correlate with patient outcome data?
- If you generate a new mutation not seen before, can the tool predict what the actual molecule will behave?

Translational: blood and tissue

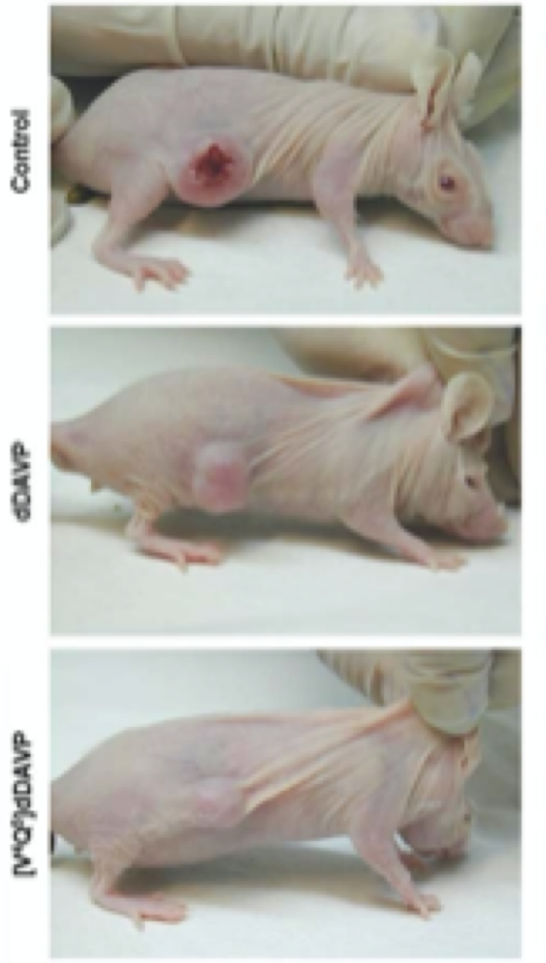


- After treatment of a GIST patient with a KIT blocker such as imatinib, can you find changes in the blood of a patient that show the drug is working?
  - Amount of free-floating DNA from the tumor in the blood
  - Evidence of tumor cells in the blood
- Is the medication having an expected effect in the tumor?
  - Amount of drug in the blood
  - In a biopsy of the tumor before and after treatment, is KIT turned off? Does this fit for how much of the blocker remains in the blood?



Translational: animal models

- Can a sarcoma from a patient grow in a mouse?
- If you treat the mouse with a tumor the same way you treat a person, does it do the same thing?
- Can you predict what will happen to a person based on what happens to mice carrying the human tumor?
- Can you genetically engineer a mouse to create the same type of tumor seen in people?
- Are there companion animals that get the same kind of cancer as people, and do they respond to treatment the same way as in people?
    - Osteosarcoma: greyhounds, larger breeds
    - Angiosarcoma: Labrador retrievers
    - Histiocytic sarcoma: Bernese mountain dog



How is progress made in research?

Trajectory of research

- Function of many variables
  - Need a good question
  - Technology: fuels new areas of research
    - Genomics, big data, large scale screening
  - Need reliable skills / hands: the craft of the work
  - Increasingly need to rely on people with different types of expertise to answer a question
    - Problem: everyone does not know what everyone else does, nor can they troubleshoot or know if the work is truly valid or not
  - Funding, explicit or implicit

Key areas of progress

Basic science

Genomics
Working with big datasets
Epigenetics
Protein signaling
Metabolism
Immunology
3-D structure with cryoEM

Translational

Mouse modeling
Organoids, avatars
Cell free DNA from blood
Single cell sequencing
Medication screening

Clinical, epidemiologic, policy

Growth of pharma trials
Immunotherapy
Crowdsourcing studies
PRO: patient reported outcomes
SEER, NCDB
Adaptive clinical trial design
FDA Accelerated approval

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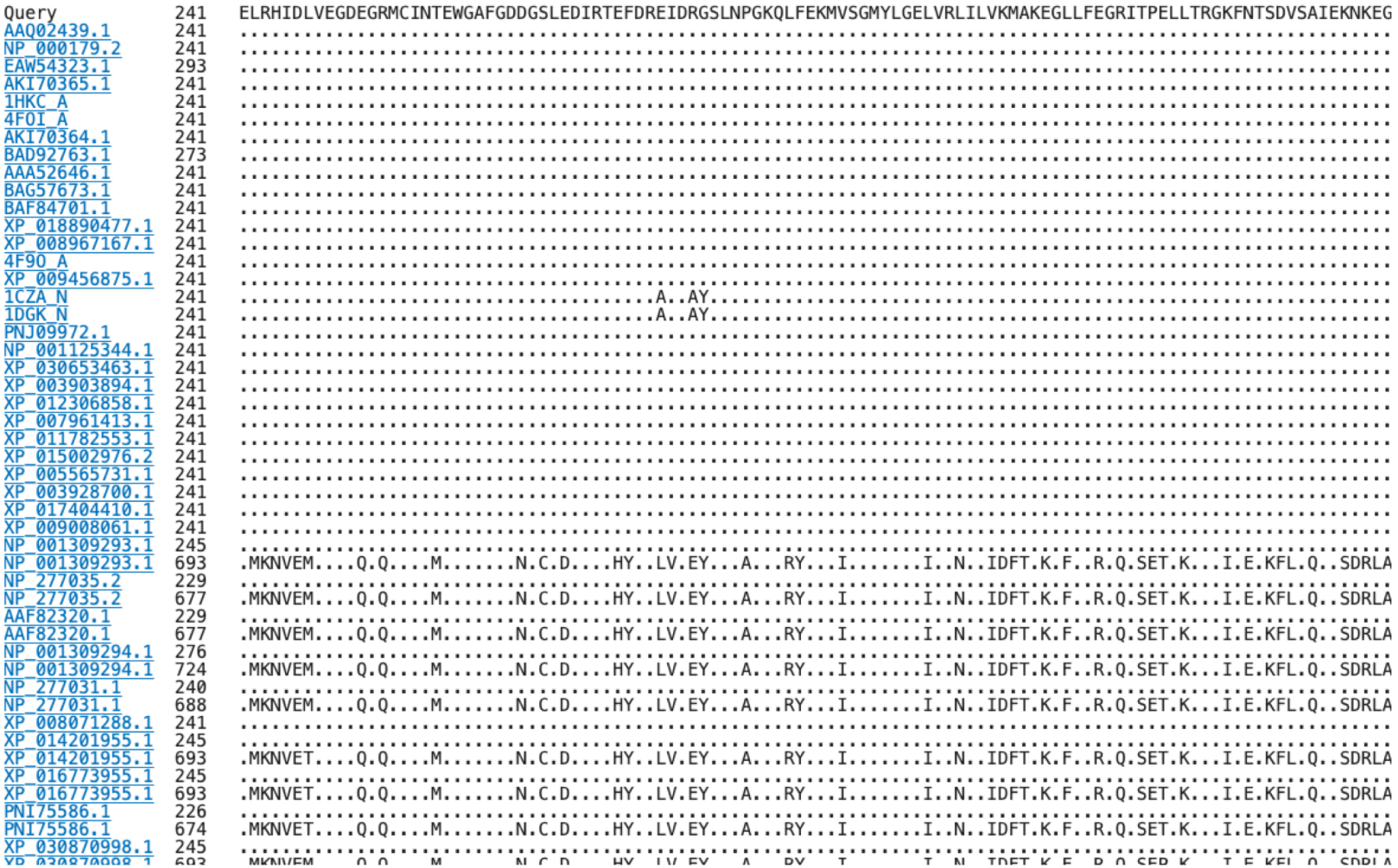
[example 1] 3-D structure by cryoEM

3-dimensional structure of a protein by cryo-electron microscopy

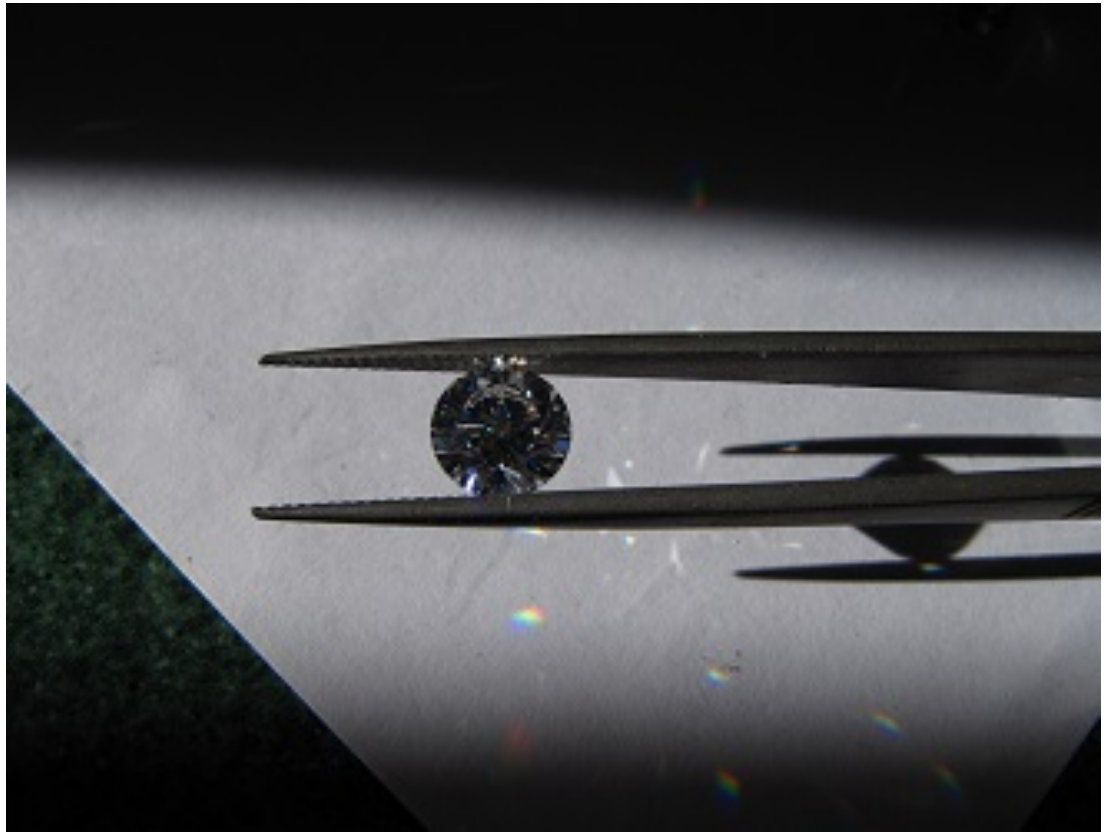
Why bother to know the structure?

- Understand how a molecule works
- Since nature repeats herself, you can use what you know about one molecule to make a hypothesis about how another molecule works
- Design molecules that change the function
  - Enhance
  - Block
  - Other changes

Relatedness of hexokinase from bacteria to plants to animals to humans



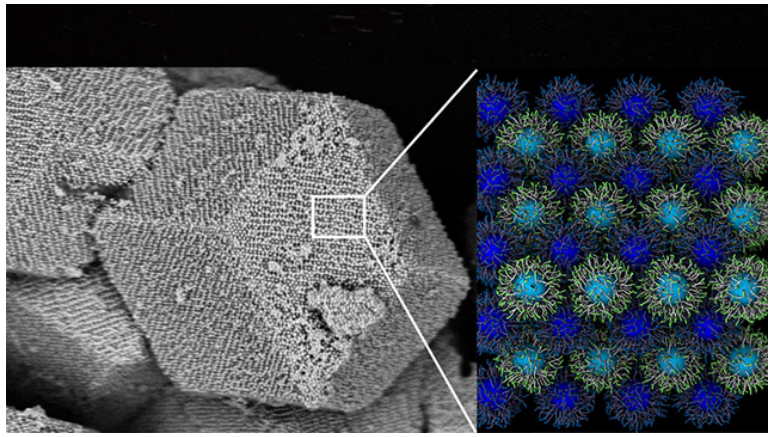
Diamond reflections



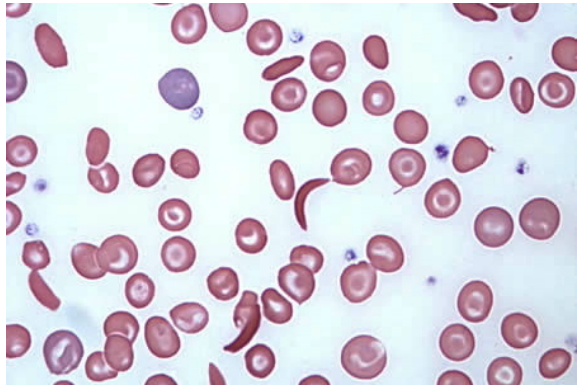
Crystals

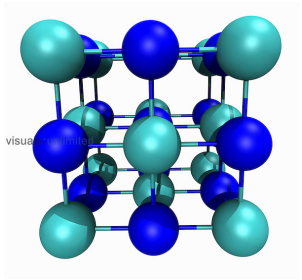
Table salt: NaCl

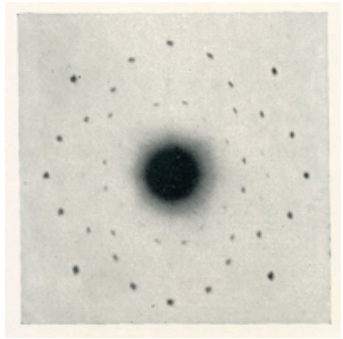
DNA



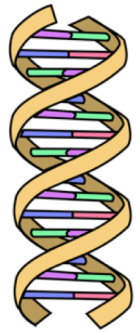
Hemoglobin

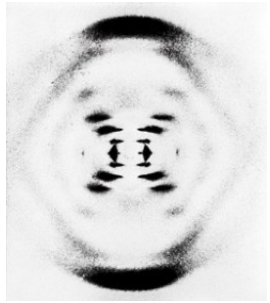


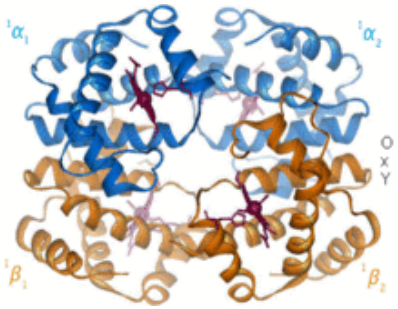


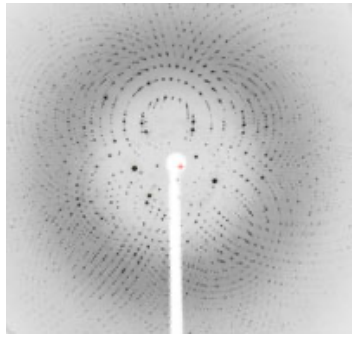


X-ray picture







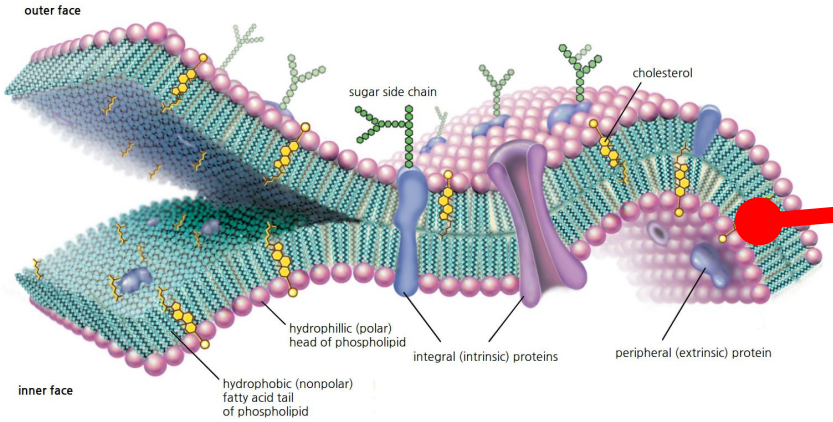


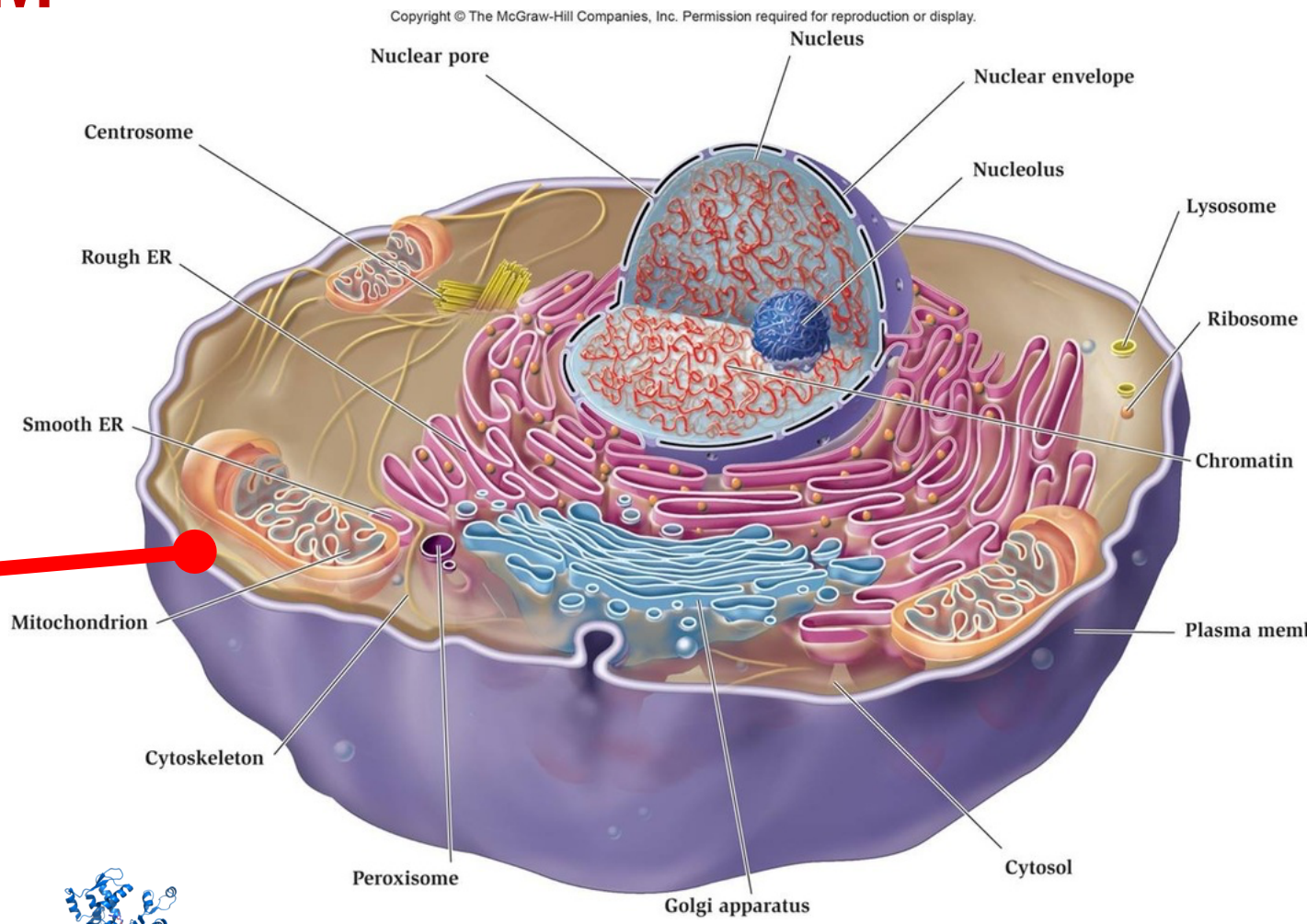
Rosenberg JM et al. Nature 1973; 243: 150

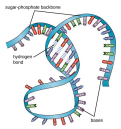
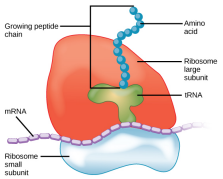
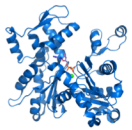
What if the protein does not dissolve in water? It’s not so easy to make a crystal.

3-D structure with cryoEM

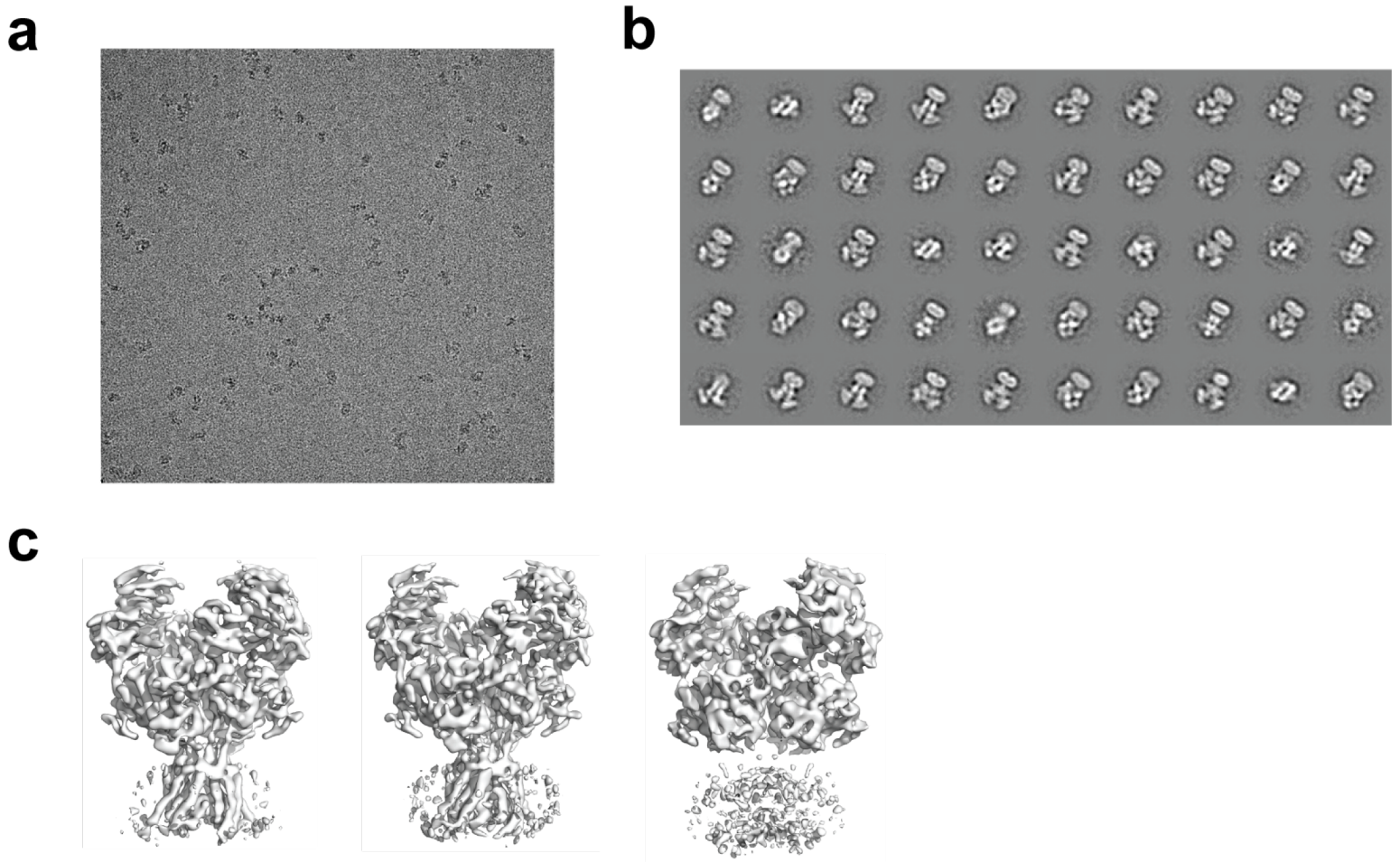
Build on the shoulders of the genomic revolution





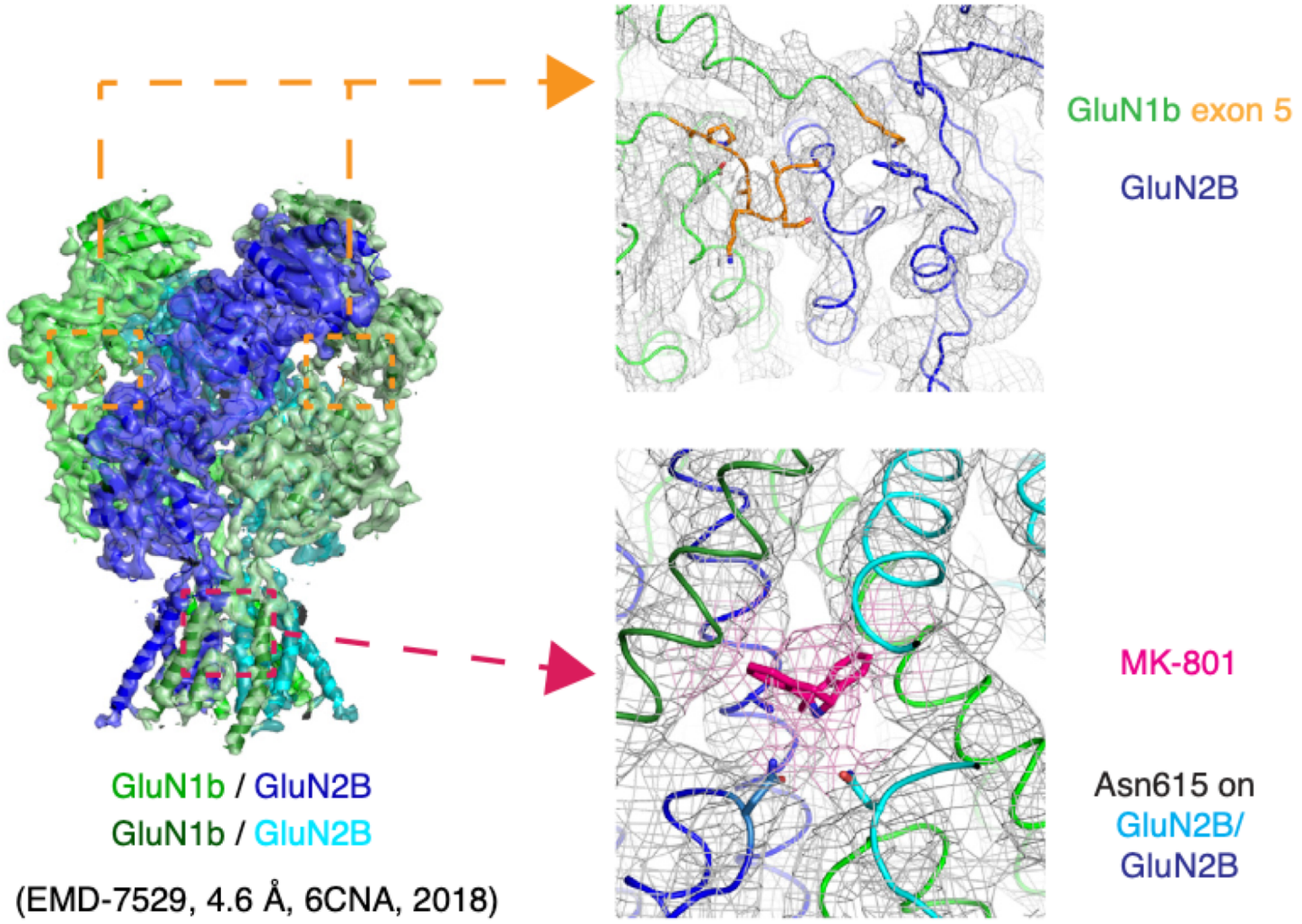
DNA →  RNA →   Protein

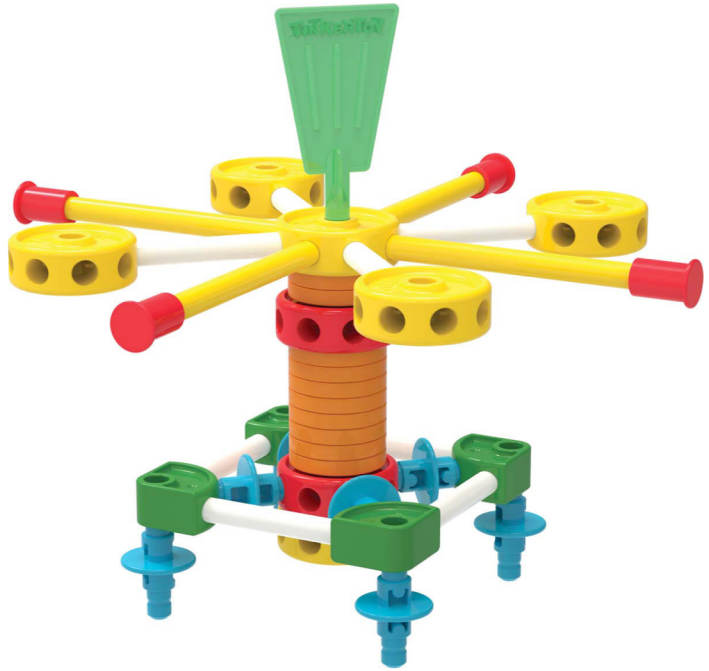
Cryo EM –proteins have a structure that can be seen without the detail of an x-ray crystal



Wang JX and Furukawa H. Curr Opin Struc Biol 2019; 54: 34

Not far off from Tinkertoys





Wang JX and Furukawa H. Curr Opin Struc Biol 2019; 54: 34

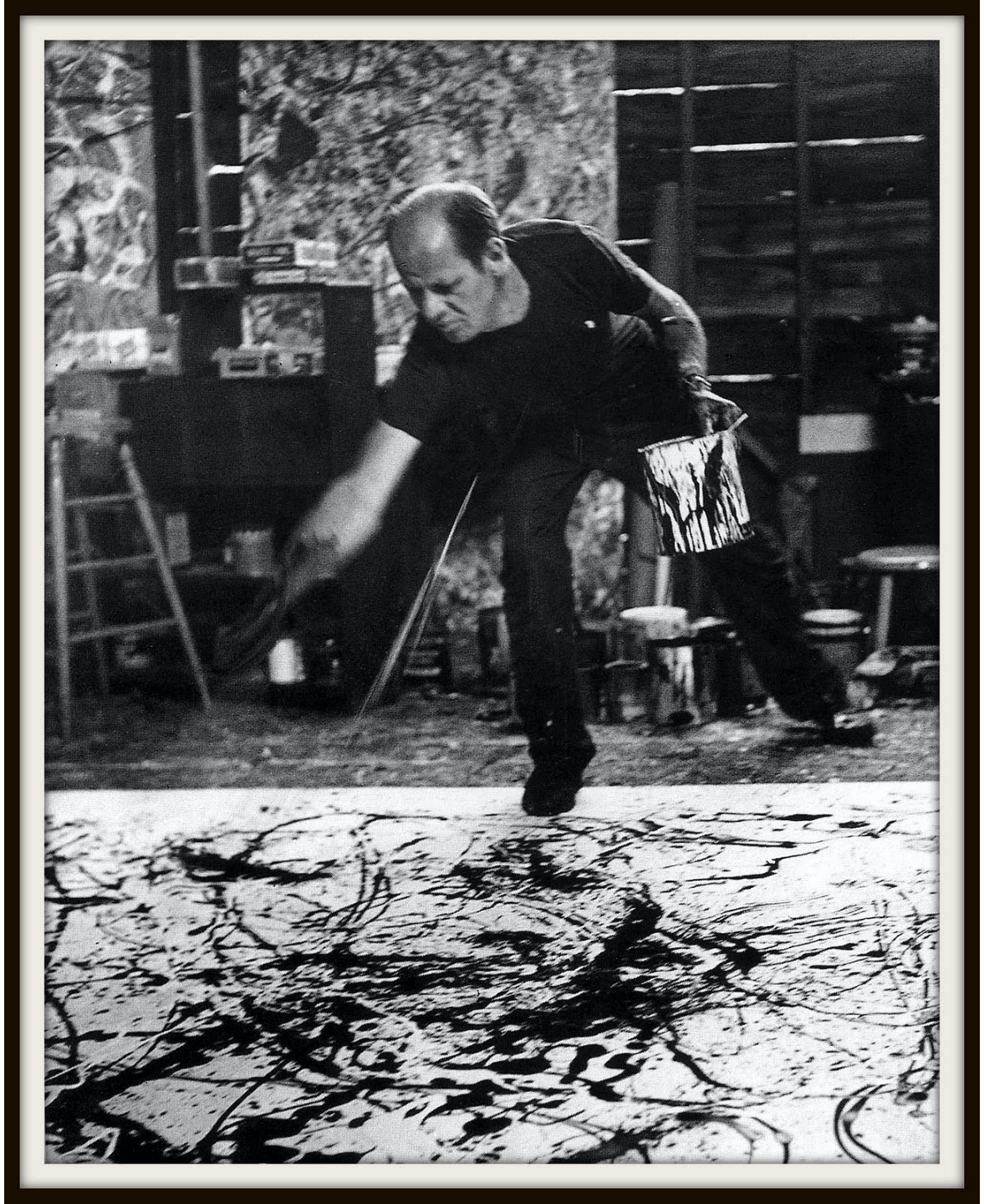
What to do then?

- We know certain sequences of amino acids (the basic unit of a protein) fold in a certain way – can guess at part of the structure based on DNA
- If you know the DNA sequence, you know the protein sequence, and can guess at part of the structure, even if it does not dissolve in water
- Once the structure is known at ATOMIC level, you can now identify or test compounds that change the function of the protein
- Does not capture if there are multiple proteins involved in a complex—
  - This too can be approached with cryoEM

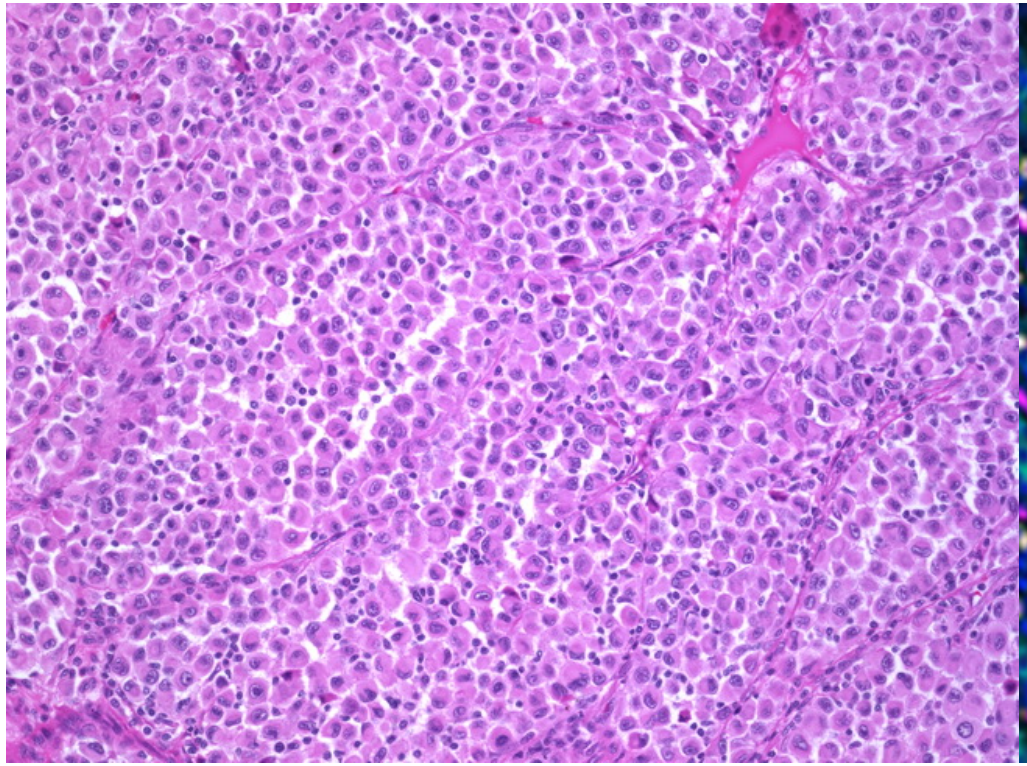
[example 2]

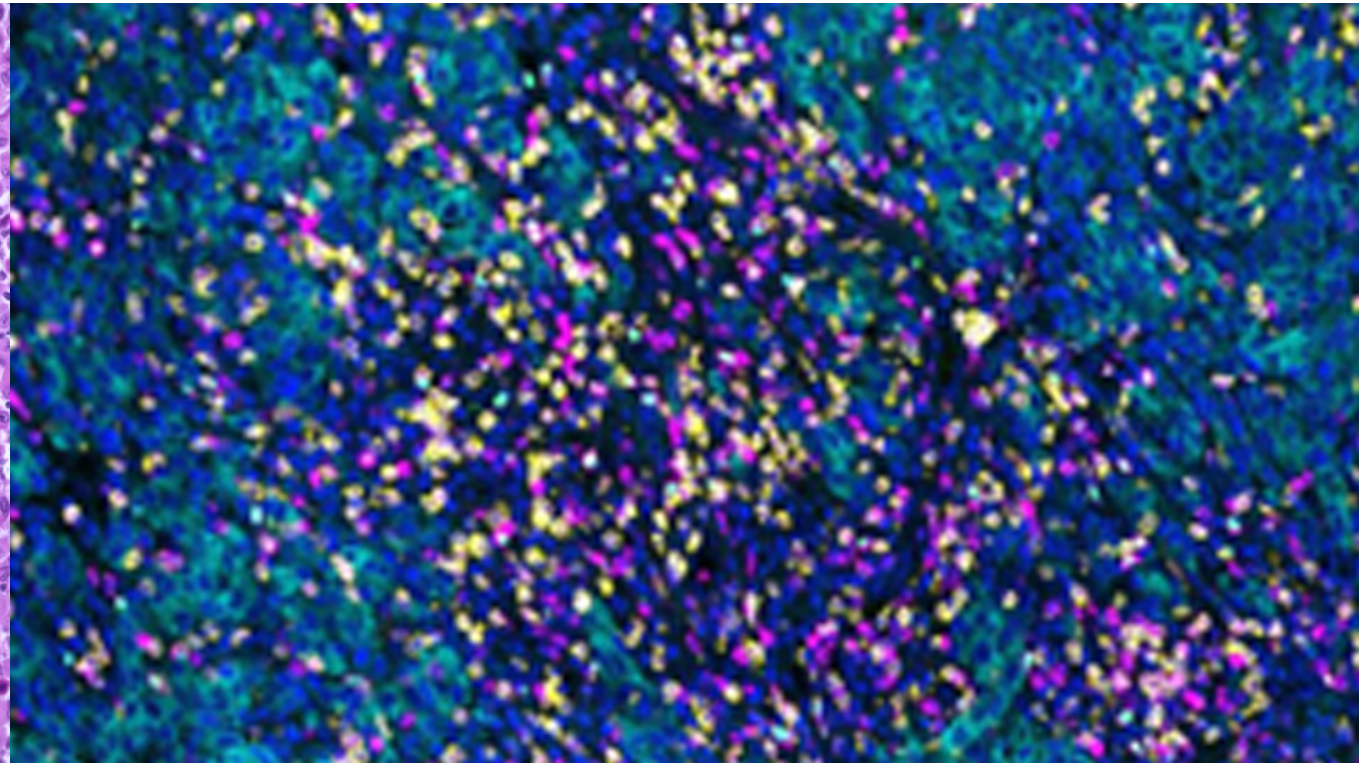
Single cell DNA/RNA sequencing

One cell at a time…together



Problem: cancers interact with a patient and involve a large number of cell types





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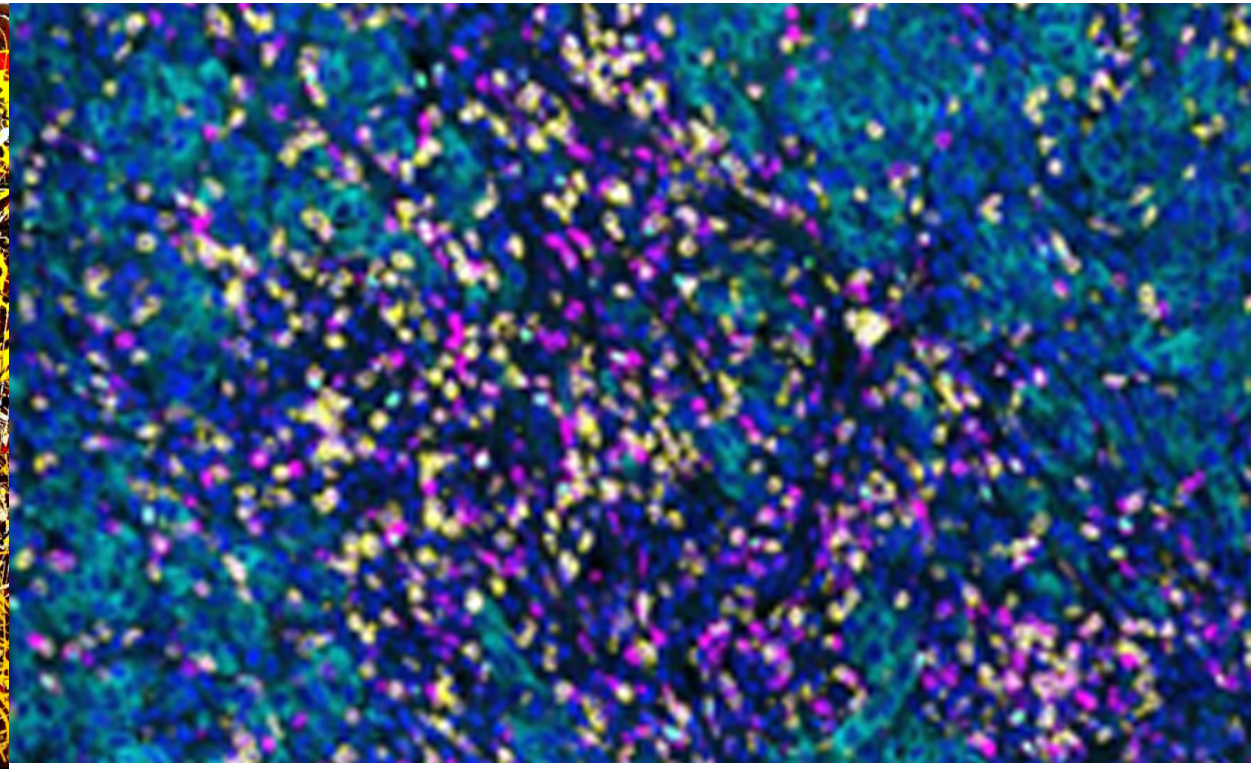
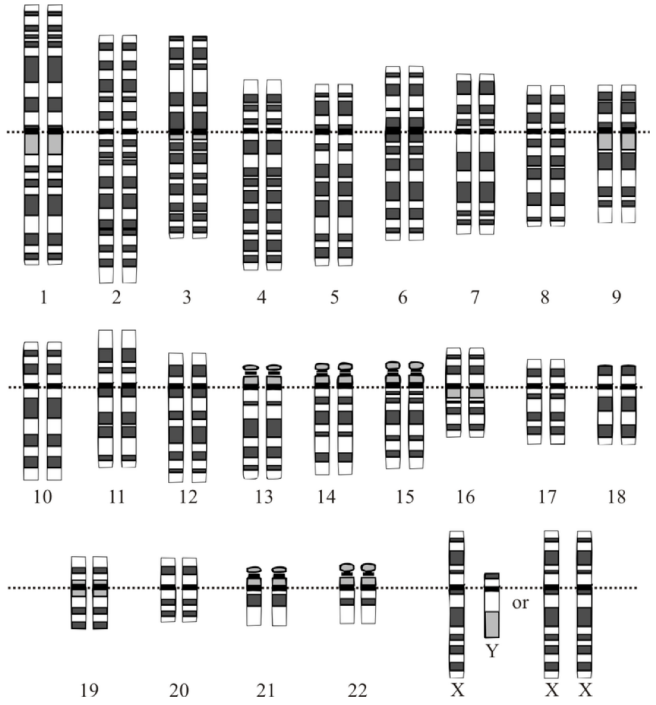


We have a road map

- Human Genome Project
- Gave us the entire DNA sequence of all 23 sets of chromosomes in a single person
- Over 3.2 billion bits of DNA / person
- Completed by and large by 2001
- More complete by 2004
- Still not 100.000% done in people

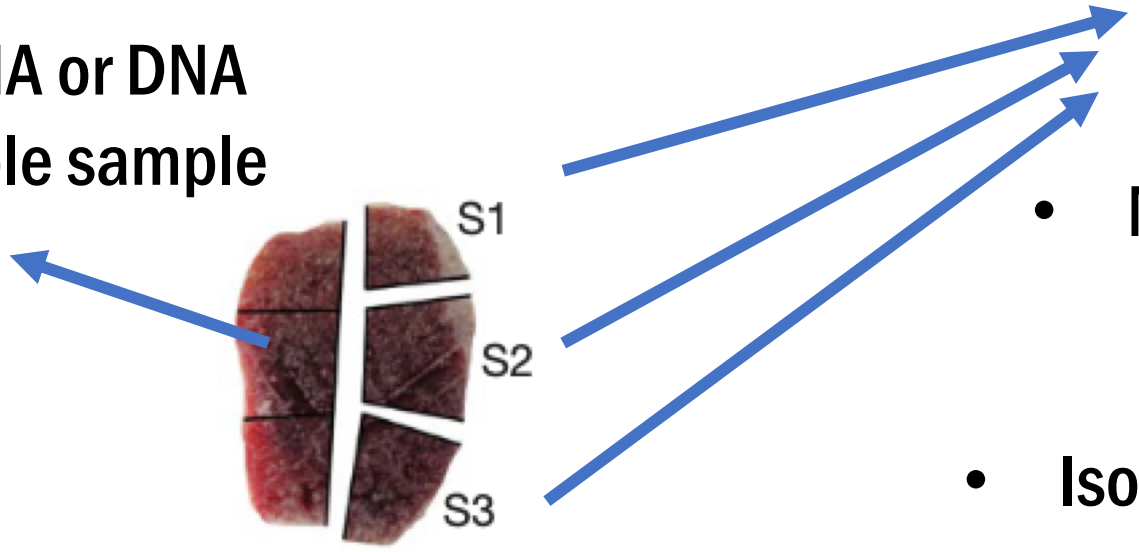


So what?

- We have about 40,000-50,000 DNA genes
- The temporary version of DNA, called RNA, can be sliced and diced into many, many more versions, which can be read by ribosomes and turned into protein
- Less than 2% of all 3.2 billion bits of DNA are read into protein via (m)RNA
- The rest of the genes make RNA that turns other genes on and off
- The RNA and proteins of a cell determine what the cell does
- If we can sequence the RNA of a single cell, we know better what the function of that cell is, and of its neighbors, and at least guess at how they act together

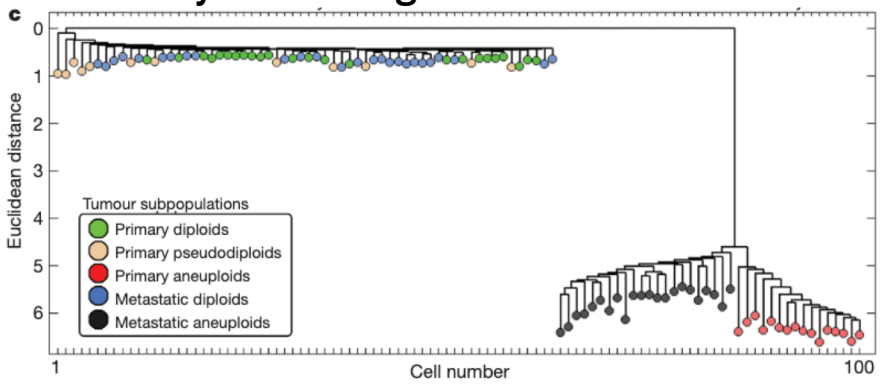
Single cell sequencing: RNA or DNA

Make RNA or DNA
from whole sample

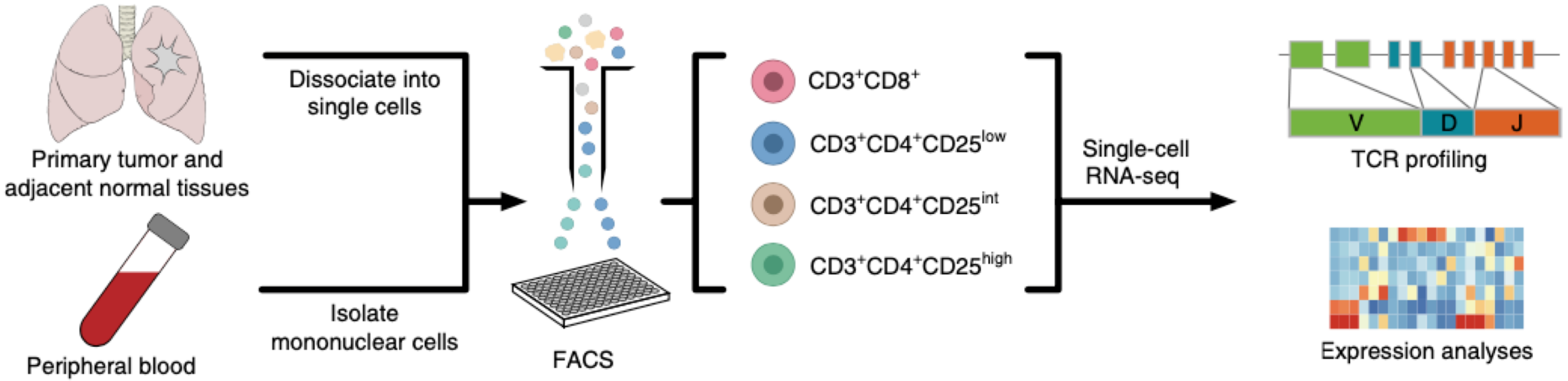


- Divide up into parts
- Make single cells from each part (millions)
- Isolate 100 individual cells from each area and make DNA and RNA, and sequence small portions of them
- Compare 100 cells from each part with the large tumor part and each other

Family tree of single cells from the tumor



Single cell sequencing: RNA or DNA

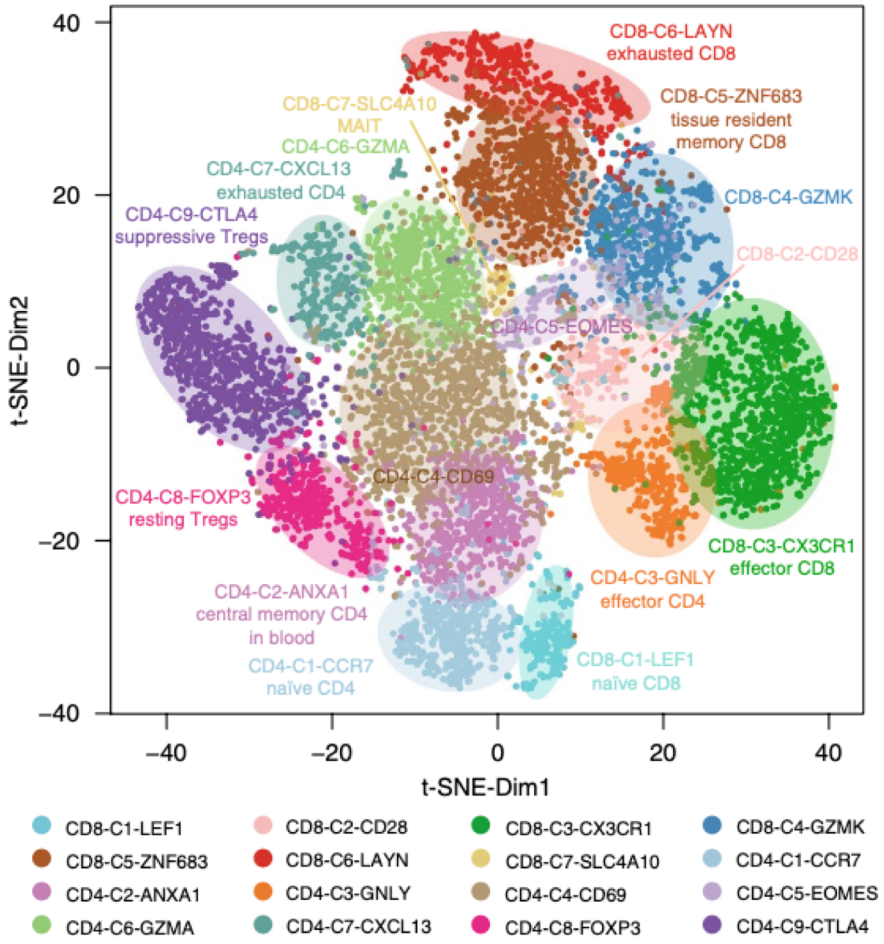


Guo X et al. Nature Medicine 2018; 24: 978

Looking at 500-1000 different cells

- Don’t look in such detail as you might with a larger sample
- Find which DNA or RNA sequences are there, and how many
- Sort the data: put the cells into bins according to how similar they are to each other
  - A bit of a challenge – each cell gives hundreds or thousands of data points

Looking at 500-1000 different cells



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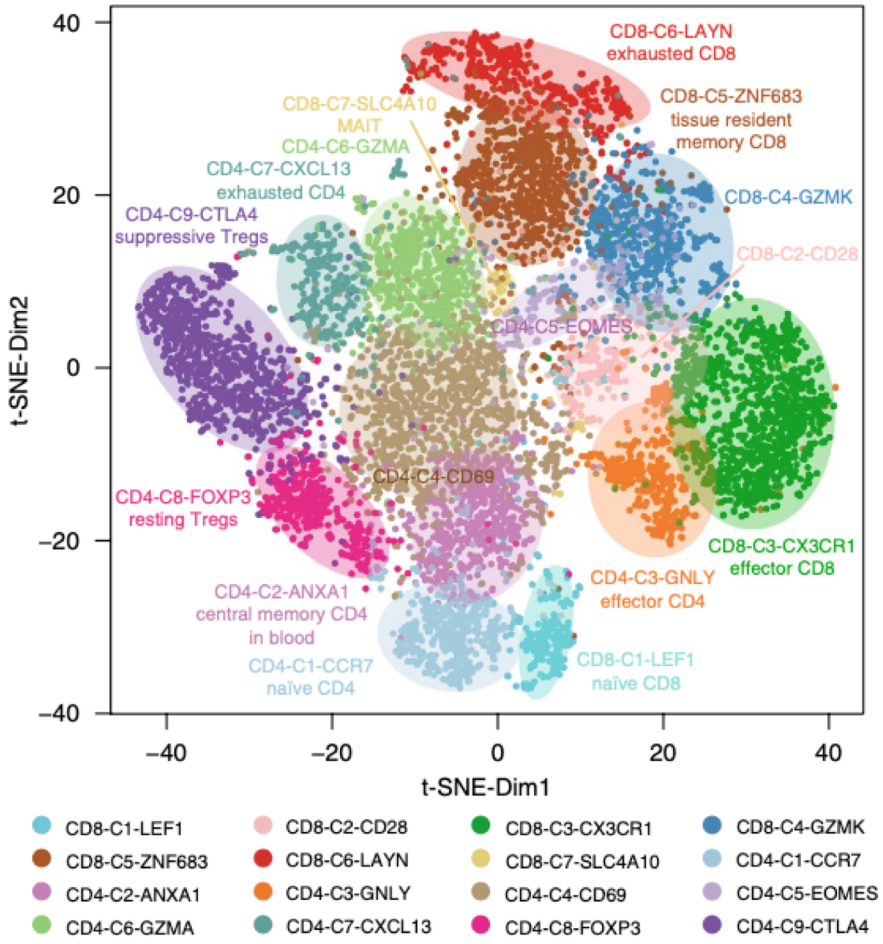


Convergence, Jackson Pollock, 1952

Guo X et al. Nature Medicine 2018; 24: 978

What next?

- How are the mutations across the tumor different?
- How do the groups of cells change with treatment…both the tumor cells and the cells of the person in which the tumor is growing
- How are resistant cells different from the starting cells?
- Which cells give rise to the tumors?

[example 3] Patient-reported outcomes (PRO)

Ask the patient, a novel concept?!

Scoring side effects on clinical trials: clinical outcomes assessments

Gemcitabine-Docetaxel ± new drug MorAb004 = ontuxizumab

TABLE 3. Treatment-Emergent Adverse Events Considered Related to the Treatment by the Investigator in ≥15% of Patients in Either Treatment Group in Part 2 (Safety Population)

Preferred Term[a]	Ontuxizumab at 8 mg/kg + G/D (n = 140), No. (%)	Placebo + G/D (n = 67), No. (%)	Total (n = 207), No. (%)
Fatigue	66 (47)	23 (34)	89 (43)
Nausea	44 (31)	15 (22)	59 (29)
Headache	42 (30)	9 (13)	51 (25)
Anemia	39 (28)	18 (27)	57 (28)
Pyrexia	35 (25)	8 (12)	43 (21)
Diarrhea	31 (22)	6 (9)	37 (18)
Thrombocytopenia	29 (21)	11 (16)	40 (19)
Edema, peripheral	28 (20)	13 (19)	41 (20)
Decreased appetite	28 (20)	10 (15)	38 (18)
Myalgia	25 (18)	5 (8)	30 (15)
Vomiting	24 (17)	3 (4)	27 (13)
Chills	21 (15)	3 (5)	24 (12)
Rash	16 (11)	18 (27)	34 (16)

Abbreviation: G/D, gemcitabine and docetaxel.

[a]Adverse events were coded with the Medical Dictionary for Drug Regulatory Activities, version 14.1.

Jones RL et al (includes RGM) Cancer 2019; 125: 2445

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the ileum. **Navigational Note:** -					
Ileus	Asymptomatic and radiologic observations only	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated; tube placement indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents. **Navigational Note:** -					
Intra-abdominal hemorrhage	-	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity. **Navigational Note:** -					
Jejunal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site. **Navigational Note:** -					
Jejunal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall. **Navigational Note:** -					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum. **Navigational Note:** -					

Blood and lymphatic system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					

Defining adverse event relationships

Clinical Toxicity	Grade	IND related?	Other drug?	Disease ?	Lab toxicity	Grade	IND related?	Other drug?	Disease?
Mouth sores	2	4	1	1	Hb 8.1	2	2	1	4

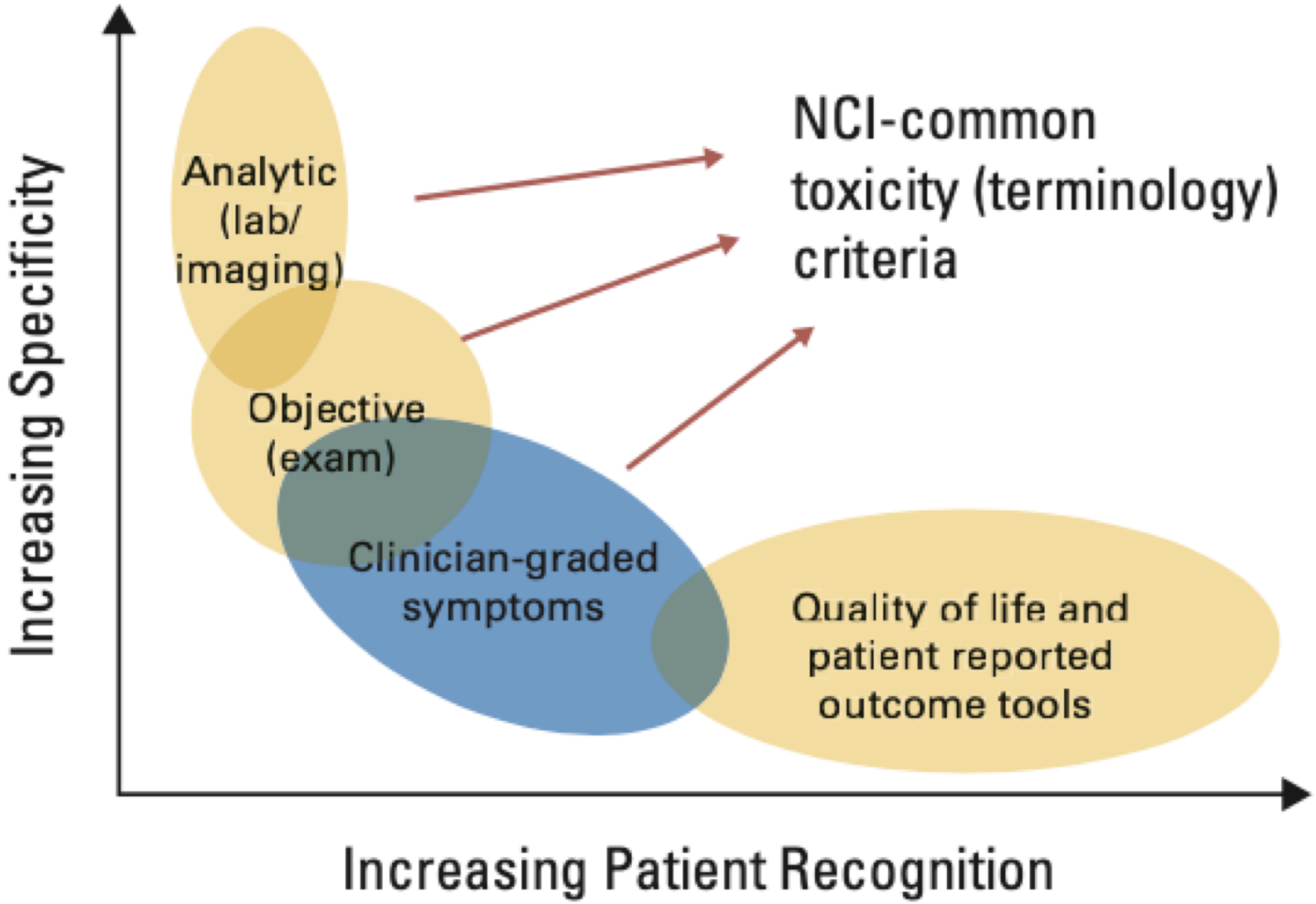
Attribution: 1. Unrelated 2. Unlikely 3. Possible 4. Probable 5. Definite

What to do?

- Under-reporting side effects means that the dose given to people may remain too high for general use
- Are we missing side effects early, before they become a more severe problem and require hospitalization?

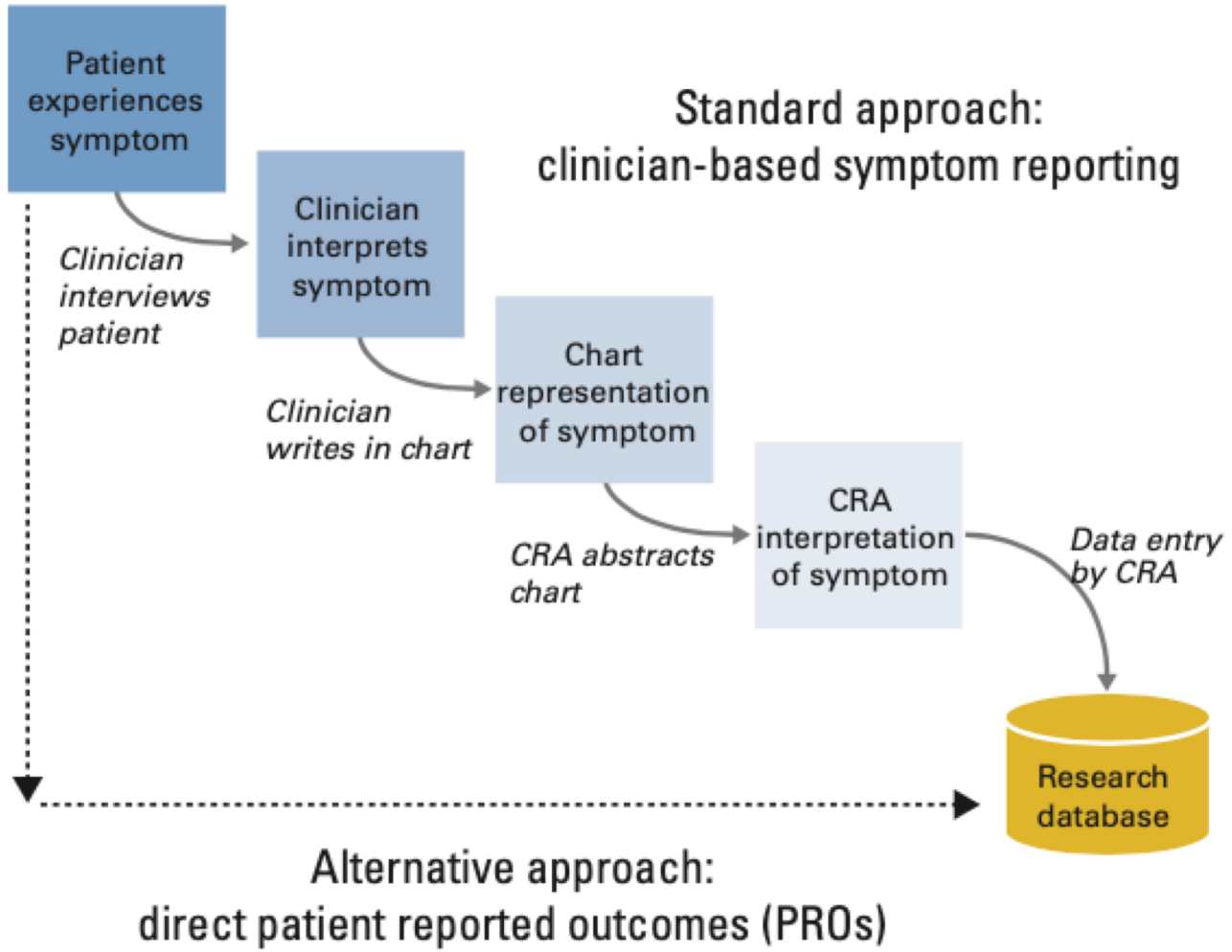
- Time is a precious commodity during clinic – missing info
- Is there time to communicate the data up the chain of command?

Let's recognize what we are seeking



Bentzen MS et al. Semin Rad Oncol 2003; 13: 189

How can we measure more accurately?



Trotti A et al. JCO 2007; 25: 5121

CTCAE → PRO-CTCAE

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE™) ITEM LIBRARY (Version 1.0)

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	A
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

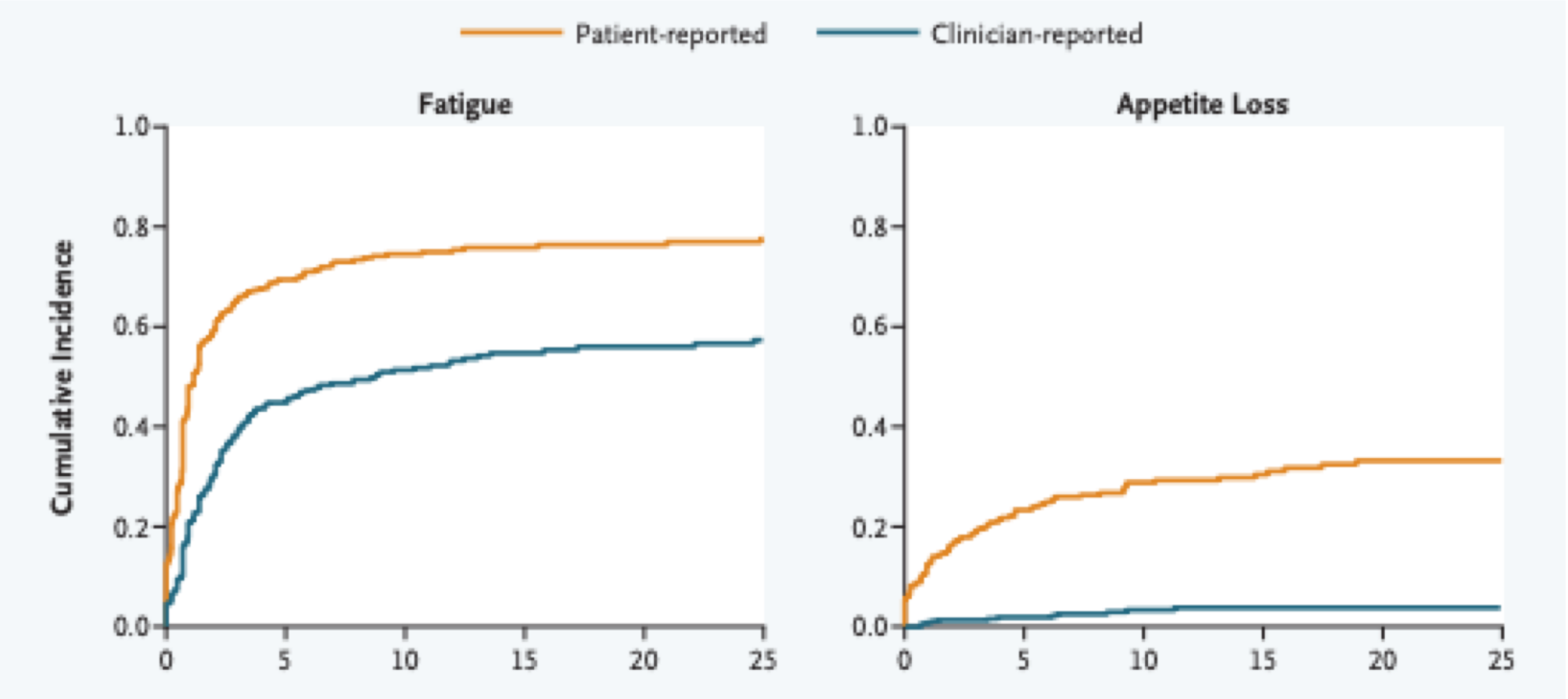
Gynecologic/Urinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	A
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	FI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

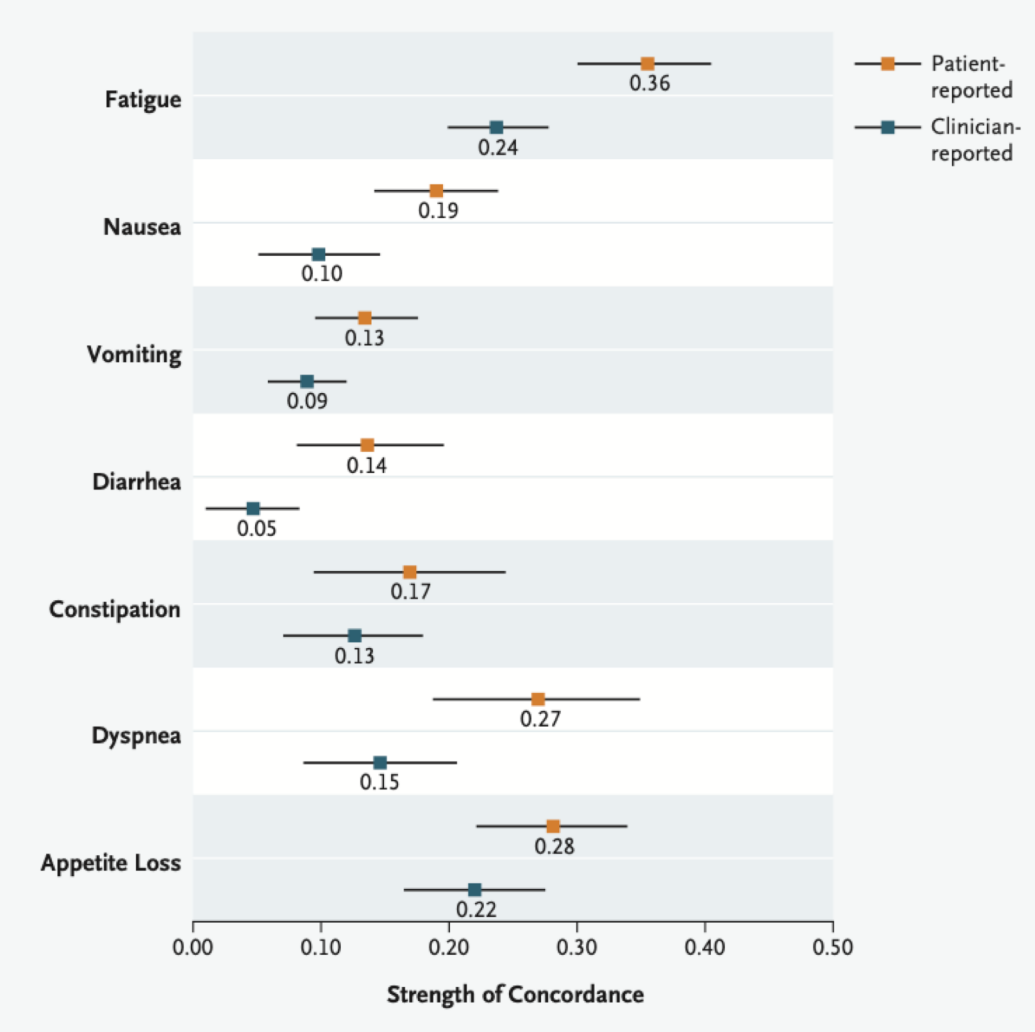
Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence
A: Amount	

Example of differences in reporting



Basch E et al. NEJM 2010; 362: 865

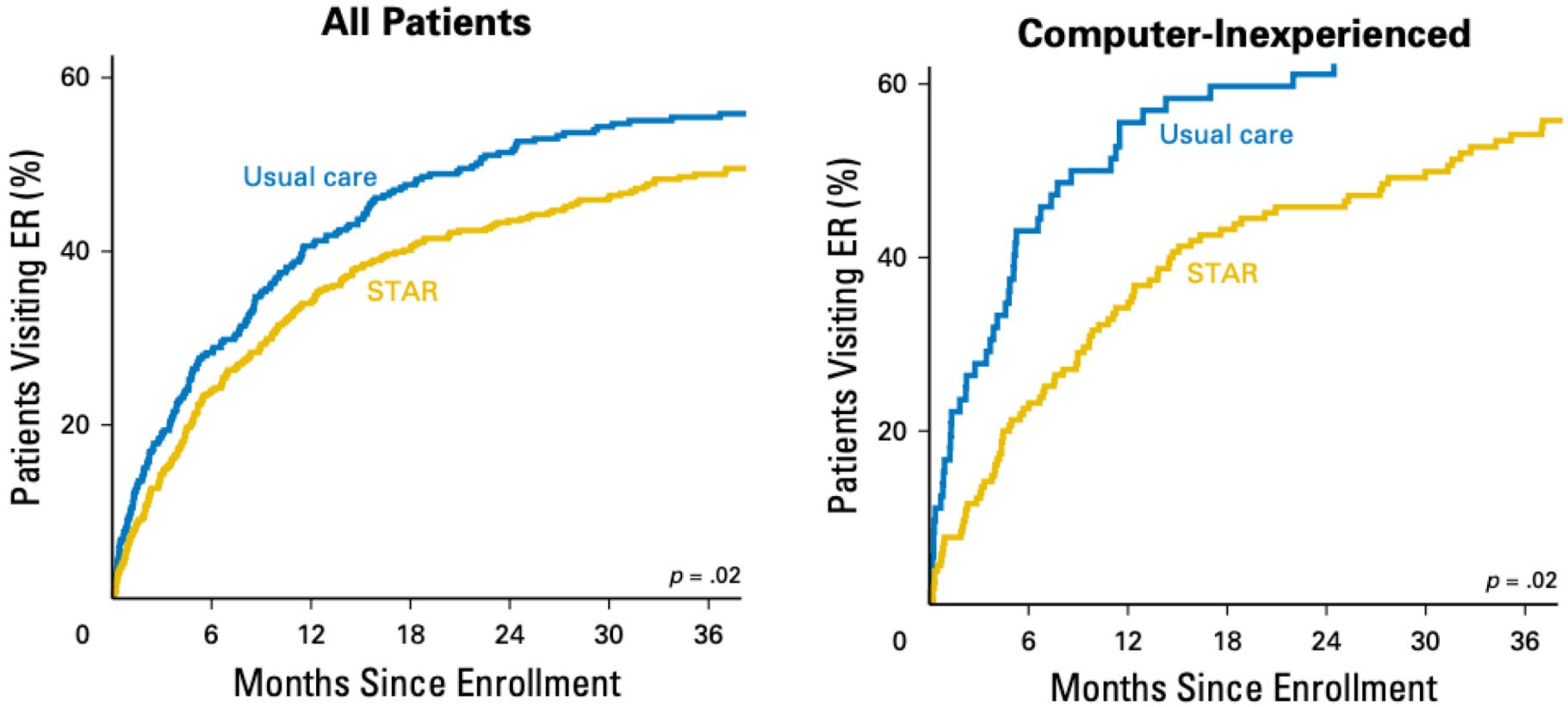
PRO: Many more side effects get reported



Basch E et al. NEJM 2010; 362: 865

It's not just completeness of data...

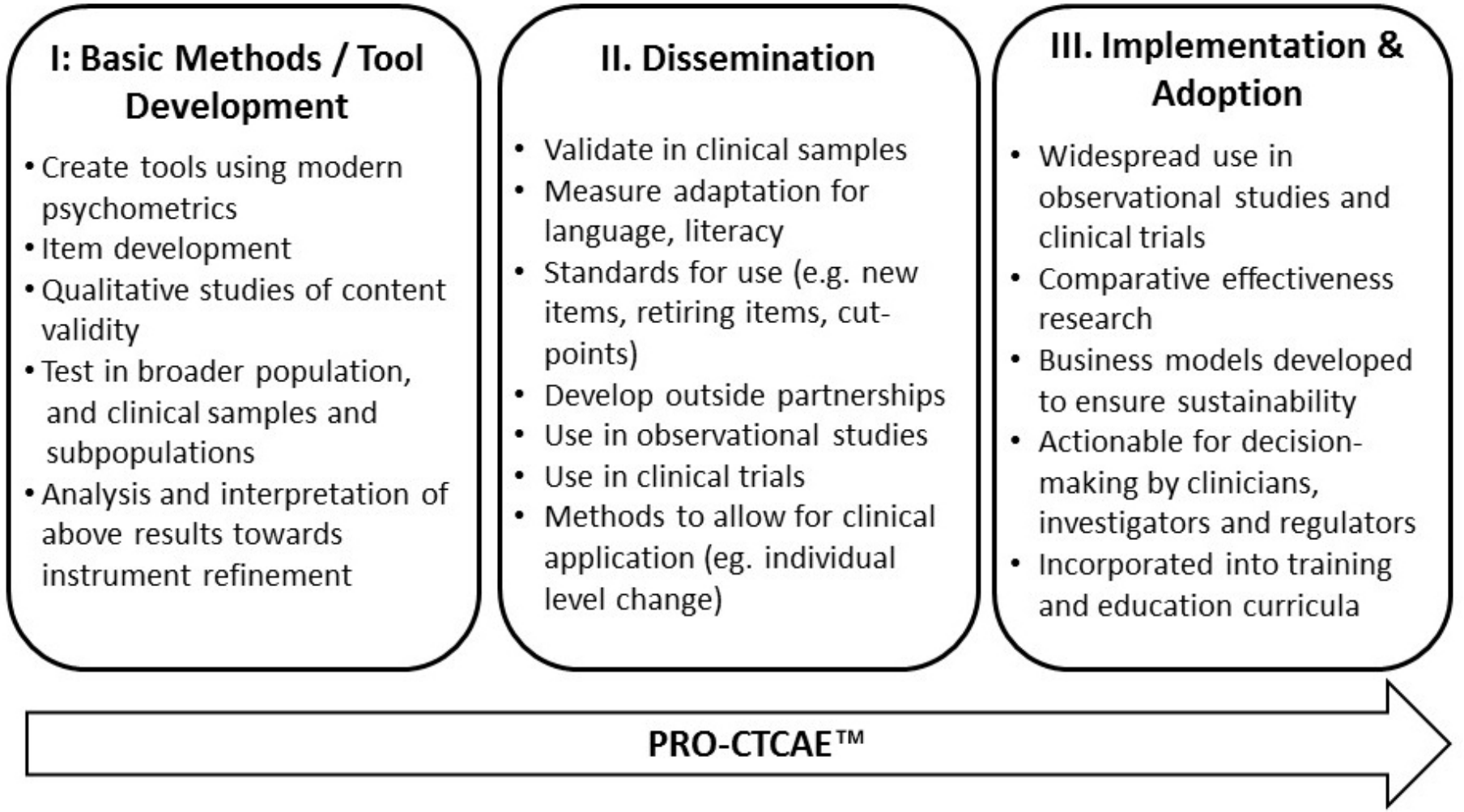
n=766



% alive at 1 year: STAR program: 75%
Usual care: 69% p=0.05

Basch E et al. JCO 2015; 34: 557

PROs are here to stay



So…what's wrong with research?

- Clinical trials that are not reported
  - Why did patient, hospital, (and company) bother?
  - Disservice to all involved
- Basic and translational work that cannot be reproduced
  - As low as 10-12% in one analysis of laboratory work
- Clinical trials have become absurdly expensive
- Me-too drugs can make money, while new ones are much riskier
  - e.g. new antibiotics
- Many papers in famous journals remain poorly cited – so maybe not as important as we thought?
  - Poor recognition of what has been done, from people writing up new studies
- Research support for the in-crowd
  - Those who sit on study sections and insure their own work's support
  - It is nearly impossible to be objective when only 5% of projects are supported
- Repetition of work (e.g. trials) asking the same questions, competing interests

Rx – how to fix ?

- Asking the right questions
  - Making resources generally available when possible (genomics, clinical trials data)
  - Duplication: Insure your question has not been answered
    - Review and cite appropriate literature
    - Requires strong mentorship
- Charge companies for access to federally supported data or resources (FDA)
  - Waiver as a function of profit status of entity
- National groups in Europe and in US provide a cost-effective means for conducting trials
- Lack of publication of results
  - How to incentivize or penalize?
- Me-too research, competing interests
  - How do we distribute national resources
    - Support for epidemiology vs cancer clinical trial vs vaccine research vs dementia vs CHF vs …
- Better education for patients regarding research and its benefit to them

What are positive changes for sarcoma research in 2020?

- Unprecedented benefits of understanding genomics and from the increased use of tools involving big data
  - MSKCC cbioportal, COSMIC mutation database
  - Other genomic resources on line: GEO, CGHub
  - Clinical trials data: NCTN / NCORP data archive
  - Conticanet, EuroBoNet in Europe, Multi-PI grants from NIH
- Some shared resources between centers:
  - New York: NY Genome Center; NY Proton Center
  - NKI pediatric oncology

What are positive changes for sarcoma research in 2020?

- Biology of sarcomas can inform treatment of other cancers
- Clinical studies do take time, and are increasingly expensive
  - Collaboration across and in between countries to make progress
  - World Sarcoma Network
  - Better connections between national groups over time
- Support for trials
  - Sarcoma investigators are efficient with use of what support they get
  - Advocacy groups are extremely important for crowdsourcing funds to support work in rare diseases
  - Attach on where possible to trials in more common diseases

Your support is critical as we move forward in research in rare cancers

Success?

Crooke

Hook

Thank you for the opportunity to speak here today

Blue Poles, 1952