

Patient Engaged Research in Gastroesophageal Cancer

Adam Bass, MD

Dana-Farber Cancer Institute

Associate Professor of Medicine; HMS

Associate Member; Broad Institute

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Summary

- A summary of the ideas behind cancer genomic profiling, as it relates to clinical care and guiding therapy
- Opportunities to complement standard genomic care with engaging in patient-directed research

Changing Paradigms of Cancer Therapy

- Traditional approach:
 - Mix/match different chemotherapy drugs by trial and error
- New approach:
 - Understand what drives each cancer
 - Attack the driver
 - (or Attack the ‘weakness’)

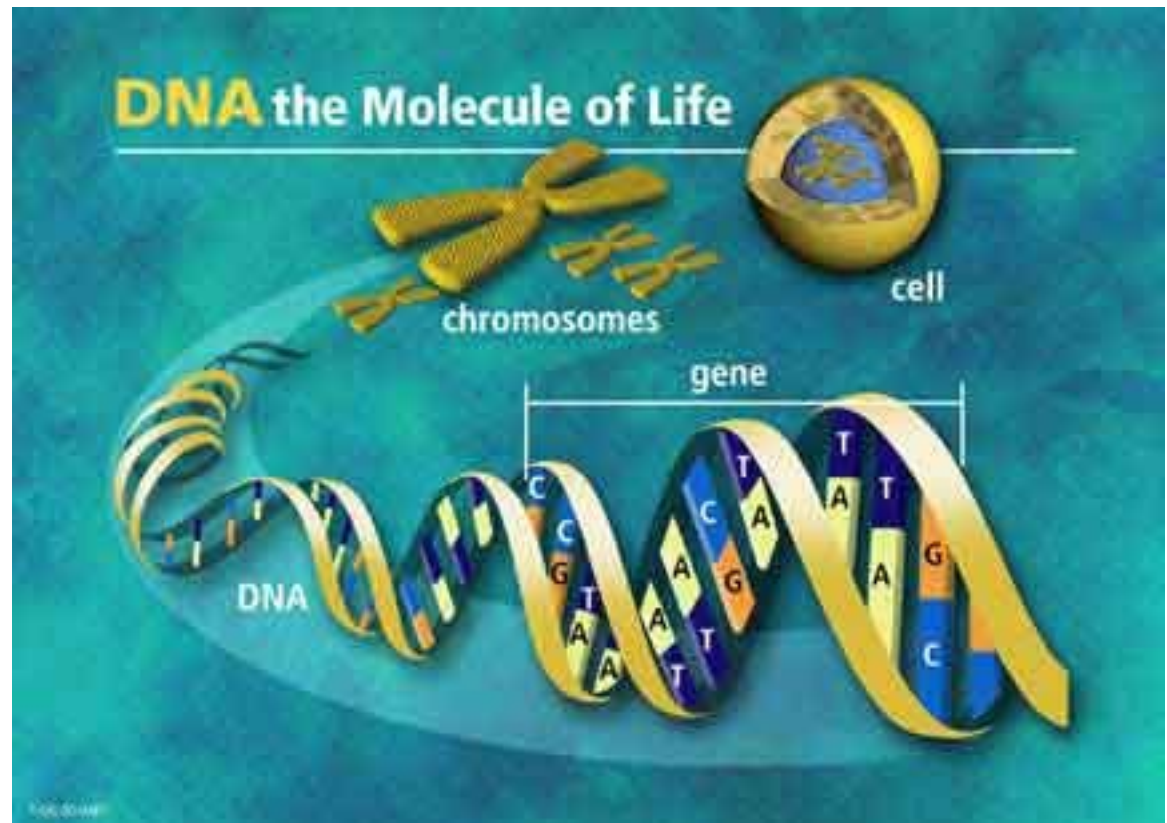


The Genome: 'Looking Under the Hood' of Cancer

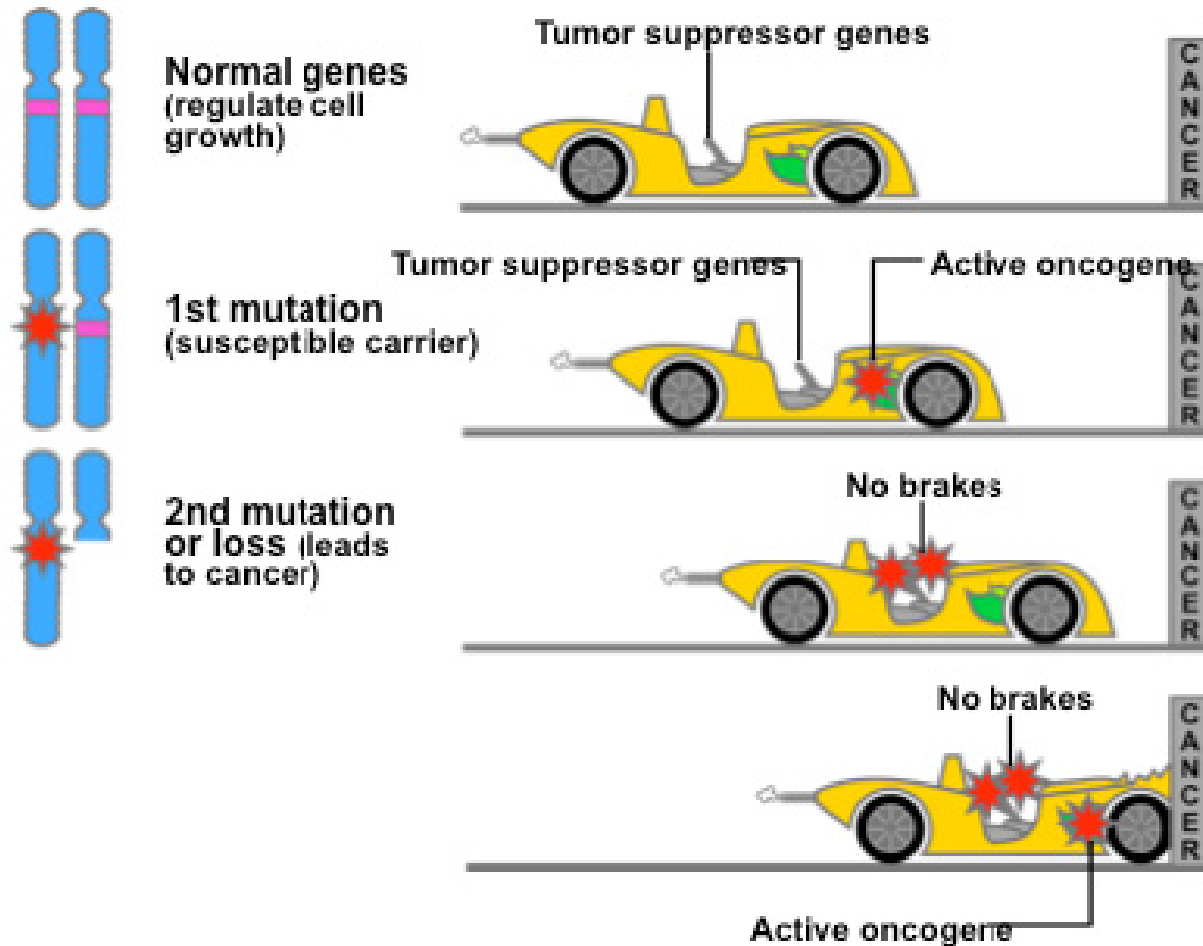
Genome = DNA in the cell

Strings of 3 billion letters (A,C,G,T) separated into different DNA pieces or chromosomes

The letters of the genome are assembly instruction for the proteins that do the work of the cell



Cancer is Caused by Genetic Mutations That Cause Cells to Grow Out of Control....



Somatic Vs. Germline

What Types of Genomes Are We Talking About?

- Somatic Alterations
 - Acquired changes (mutations) in the DNA that were NOT inherited
 - How the cancer DNA differs from DNA of normal cells
 - Most cancer genes are somatically altered
 - Most therapeutic targets are being guided by these kinds of genomic alterations
 - These are NOT alterations that are passed down to kids
- Germline Alterations
 - Inherited DNA variations (in all the cells of the body)
 - E.G., *BRCA1* in breast/ovarian cancer
 - Most GI cancers are not caused by these inherited cancer syndromes

Types of Somatic Alterations in the Cancer Genome (DNA)

- Mutations (Typographical errors in the letters)
 - E.G., *KRAS*, *BRAF* mutations.
- Amplifications/Deletions (Changes in copies of a gene)
 - Range from extra copy of a whole chromosome to dozens of extra copies of a small region with just a single gene
 - *ERBB2* Amplifications in GE/BC → Trastuzumab sensitivity
- Translocations (Linking together two genes)
 - Can be between chromosomes (e.g. BCR/Abl in leukemia) or within a chromosome (EML4-ALK in lung cancer)

Why Genomic Profiling Will Increasingly Guide Cancer Therapy

- Tumors become dependent upon genes activated by mutation (i.e. the gas pedals in the car)
- Drugs that effectively block these activated genes often are highly effective
 - But different patients have different activated ‘genes’
 - Therefore different patients with the ‘same’ cancer may need different drugs!
- Big idea: Genomic profiling of each patient’s cancer may help us find out what is driving each tumor and therefore may help us select optimal targeted drugs for each tumor.

Other Ways that Genome Profiling Can Help Guide Therapy

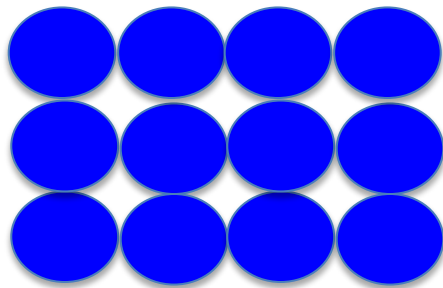
- There are emerging ways to use these data beyond finding specific cancer 'Drivers' to target
- Specifically, the pattern of mutations can point to other weaknesses in cancers that can inform therapy
 - Example: tumors with microsatellite instability are often good candidates for immune-therapy
- There is new research on the potential of finding cancer DNA in the blood (cell-free DNA) to help predict risk of cancer recurrence after surgery and to help guide therapy in advanced cancer

Targeted Therapy is NOT Gene Therapy

- Genes are the recipes for proteins
 - KRAS gene is the recipe for KRAS protein
 - Proteins do the ‘work’ of the cell
 - Mutant genes make abnormal protein
- Drugs (almost always) block proteins
- Targeted therapies target proteins
- So we are not treating the genes
 - The genes are the indicator of which protein to target

Genomic Profiling of Cancer

- Can put patients into meaningful groups
 - Also sub-subtypes with specific key gene changes → implications for therapy



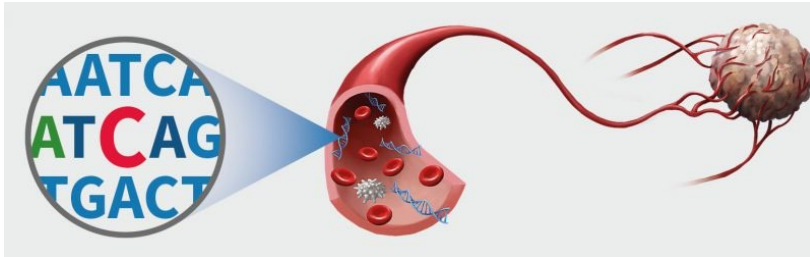
Ways to Test Genetic Features of Cancer To Help Guide Therapy

- What we need to consider
 - What to test?
 - Primary Tumor, Metastatic Tumor, Blood/Plasma...
 - When to test?
 - At diagnosis, at progression of disease....
 - How to test?
 - Focused tests for single gene, gene panels, whole genome or whole 'exome' sequencing

What To Test

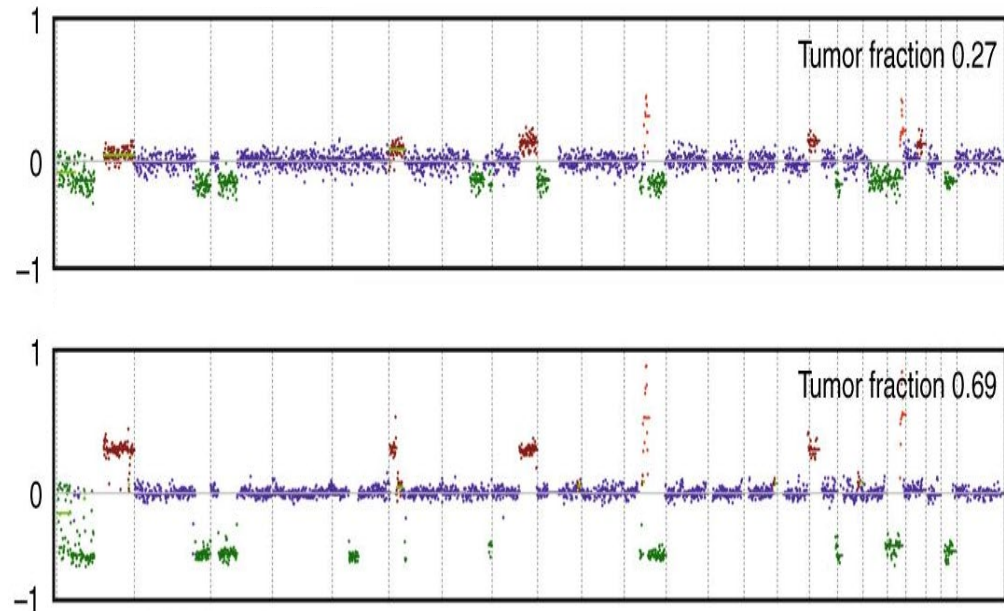
- The vast majority of cancer testing is done on tumor tissue
 - Samples from surgery or biopsies are embedded in wax blocks to preserve them. DNA can be isolated from these
 - Samples can be from primary tumor or from metastatic lesions
 - When you test a tumor sample, you are learning about the DNA only in the sample you are testing
 - In other words, if the tumor varies in different locations (is heterogeneous) key information can be missed

New Tools To Study Cancer DNA: "Liquid Biopsies" from the Blood



Slide from Inivata

Example how
cell-free DNA
can find what
is seen in
tumor tissue



cfDNA
0.1x WGS

Tumor
1x WGS

Cell-Free DNA: Advantages and Disadvantages

- **Advantages**

- Getting blood is 'easy'
- Results may help find what would be missed with a single biopsy
- Can be useful for tracking tumor over time and how it evolves after therapy
- Can be useful to determine risk of recurrence after surgery

- **Disadvantages**

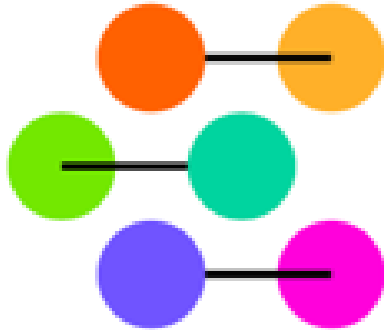
- Not all tumors' DNA can be found in plasma (example, gastric cancer with peritoneal spread often not detected)
- Even if found, the 'sensitivity' to detect specific mutations can vary from patient to patient and be less than in tumor tissue

When To Test

- Rule of thumb, do a test when the answer is going to change what you do
- Key idea to consider is that cancers do evolve (especially in response to therapy)
 - Therefore, there can be differences between results from when patients are first diagnosed and when they may be looking for additional therapy
 - Many clinical trials are now asking for new tumor biopsies to test the tumor as it is immediately prior to therapy

Pivoting to Patient-Engaged Research

Count Me In



*Enable cancer patients anywhere
to share their information and
samples with researchers
everywhere*

Challenges of Studying Patient Tumor Samples



85% of U.S. cancer patients are treated in community settings

Most patients' samples and data have not been readily available for study



Technology, social media, and cultural changes now provide a new opportunity to engage cancer patients and directly partner with them in this research

Where we are going....

 Esophageal
& Stomach
Cancer Project

[Learn More](#)

[count me in](#)

You can have a direct impact on the future of Esophageal and Stomach Cancer

If you have been diagnosed with esophageal or gastric/stomach cancer, join a nationwide initiative of patients, doctors, and scientists by sharing your tumor samples, your medical information, and your voice. Together we can develop a comprehensive resource to accelerate discoveries that may inform future therapies.



 **BROAD**
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The Scientific Need



- **Ultimate goal:** To understand what drives cancer so that we eventually can interpret every patient's cancer genome, identify the optimal treatments, and anticipate and preempt resistance before it arises
- There's been a lot of progress, but we still have much work to do
- What will it take to get there? Detailed molecular and genomic characterization of **thousands** of tumor and germline samples along with clinical, pathologic, and radiologic data

What is this?

- A research study approved by the Dana Farber Cancer Institute IRB (Ethics Board)
- Patients anywhere in country can sign up online and share basic clinical information and give consent for:
 - Count Me In team to obtain clinical records to collect data
 - Count Me In team to obtain extra tumor samples from hospital/clinics and get DNA and perform genomic and molecular analysis on the tumor
 - Us to share the data (not identified to patients) across research community

How Does This Work?

- Any patient with a diagnosis of (or history of) stomach or esophageal cancer can signup
 - Enroll at escproject.org
- Take a ~5-10 minute online survey detailing treatment history
- Choose if they want to consent to additional studies
 - Allowing team to obtain and medical records and to obtain and profile tumor tissue samples (from old surgery or biopsy)
 - Provide samples of blood and saliva

Saliva?

- We send a 'kit' with container for saliva/spit.
- You fill it and mail it back to us in the package we provide
- Saliva is used as source to get normal DNA
 - Normal DNA is used as a comparison to cancer DNA
 - Normal DNA is also way to identify the genetic variations that we all inherit, some of which may associate with cancer behavior

Blood??

- Burgeoning field of cancer DNA that is ‘shed’ into blood from tumors
 - New exciting method to study cancer DNA
- We send you blood collection kits with special blood tubes for getting circulating tumor DNA
- You bring the tube to clinic during regular blood work or can get blood drawn at special participating labs (our team can help)
- Mail the tube back in the provided special envelop/kit

How do I provide records and tumor samples??

- You don't have to do anything
- If you consent, our team handles everything
 - Requesting records from the clinic/hospital
 - Extracting information from records
 - Identify if there is a sample from which we can collect material for research
 - Note, we will not deplete samples in case material is needed for future clinical testing

A Few Potential Questions

- Will my identity be revealed?
 - No, patients are listed by code number
- Will I get my data back?
 - As this is research, we are not legally allowed to report back data
- Can I withdraw consent?
 - Yes, at any time

More Potential Questions

- Will my data be sold?
 - No, data will be placed on public repositories that are used by researchers (across world, including working for government, academics and industry)
- Who is paying for this?
 - This is funded by philanthropic donations

Ways to Help

- Sign Up
 - And post on social media
- Become a patient ambassador
 - Help reach/recruit additional patients, including on online patient communities
- Participate in our working group to help develop new questions, shape how we engage with patients

jointcountmein.org/

escproject.org