Precision Oncology: Promise and Pitfalls

Victor T. G. Lin, MD, PhD
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Precision Oncology – What is it?

• The use of biomarkers to direct therapy (often targeted).

• Contrary to common belief, the broader community of oncologists has already been practicing precision oncology for quite some time without knowing it:
  • ER/PR/HER2 positivity used to determine hormonal and chemotherapies
  • Rituximab for CD20+ B-cell lymphomas
Precision Oncology – What is it?

• Precision oncology is not necessarily targeted therapy
  • Triple-negative breast cancer does better with conventional chemotherapy.

• Targeted therapy is not necessarily precision oncology
  • Cetuximab in head and neck cancer is not predicated on a biomarker.

• Precision oncology includes negative predictive biomarkers:
  • KRAS mutations in colon cancer are used to rule out upstream blockade of EGFR with cetuximab or panitumumab.
Precision Oncology – What is it?

• When most clinicians hear “Precision Oncology,” what they really hear is “Next Generation Sequencing (NGS”).

• What is it?

• How do we do it?

• Why do we do it?
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• Why do we do it?
NGS – What is it?

- Previously, we sequenced genes using the Sanger chain-termination method.
  - Great for single targets
  - Cheap
  - Difficult to sequence long pieces
NGS – What is it?

- NGS is a method by which we can sequence large amounts of DNA in a **massively parallel** and **high-throughput** way.
NGS – What is it?

• This is a little bit like intentionally breaking Humpty Dumpty and putting him back together again.

• Sequencing small pieces is faster, and we can do hundreds of millions of pieces concurrently.

• This is only possible with the computing power we have now.

• The Human Genome Project took 15 years. Now we can do a whole genome in days to weeks.
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NGS – How do we do it?

• There are a wide variety of NGS platforms available to clinicians:
  • Foundation
  • Guardant
  • Strata
  • Center-specific protocols
  • Etc.

• The way they differ is in what and how they test.
  • Knowing specific strengths and limitations is important to proper interpretation.
NGS – How do we do it?

**Tumor Tissue**
- Testing the actual tissue of interest.
- Possibly more confident that a negative is actually a negative.
- Requires an adequate biopsy (not an FNA).

**Liquid Biopsy**
- Samples the peripheral blood for cell-free DNA or DNA from CTCs.
- May provide a global picture in the settings of no radiographic tumor or many lesions.
- False positives (CHIP) and negatives.
NGS – How do we do it?

**Whole Genome/Exome**
- Broader sequencing.
- Good for hypothesis generation.
- More template means less read depth, slower turn-around.

**Hotspot**
- Narrowed to sequences of specific interest.
- More read depth means increased sensitivity in the hotspot regions.
- Tells you nothing about non-hotspot regions.
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NGS – Why do we do it?

• The idea is to potentially use drugs approved for other cancers or experimental agents to exploit common biologic vulnerabilities.
Precision Oncology

PROMISE AND PITFALLS
Precision Oncology – Promise

• To select patients for treatment in order to improve efficacy and outcomes.

• To spare patients from toxicity wherever possible.

• Responses can be rapid and very dramatic, particularly in cases where alternative therapies are known to be ineffective.
Precision Oncology – Promise

• Vemurafenib in a patient with widely metastatic BRAF V600E melanoma (Wagle et al, JCO 2011).
• Widely metastatic salivary ductal carcinoma with a complete response to dabrafenib and trametinib (Lin et al., JNCCN 2018).
Precision Oncology – Promise

• The success or failure of this approach depends on two major factors:

The **RIGHT DRUG** and The **RIGHT TARGET**
Precision Oncology – Promise

Our successes are all characterized by having both:

**APPROVED:**
- ER/PR+ Breast Cancer: tamoxifen, letrozole
- HER2-amplified Breast/Eosophageal/GEJ: trastuzumab, T-DM1
- CD20+ B-cell Lymphomas: rituximab
- BCR-ABL+ CML and ALL: imatinib
- PML-RARA+ APL: ATRA and ATO
- PD-L1+ cancers: pembrolizumab, nivolumab
- MSI-H/dMMR cancers: pembrolizumab
- BRAF V600E melanoma, NSCLC, anaplastic thyroid: dabrafenib/trametinib
- ALK-fusion NSCLC: crizotinib, alectinib
- EGFR-mutant NSCLC: erlotinib, afatinib
- EGFR T790M NSCLC: osimertinib
- BRCA ovarian: olaparib
- NTRK-fusion cancers: larotrectinib
- HL/CD30+ NHL: brentuximab
- IDH1-mutant AML: ivosidenib
- IDH2-mutant AML: enasidenib
- FLT3-mutant AML: mitostaurin

**ON THE HORIZON:**
- TMB-H cancers: ipilimumab + nivolumab
- RET fusion/mutant cancers: LOXO-292
- MET: cabozantinib, savolitinib
- Exon 20 EGFR/HER2: poziotinib, TAS6417
- PI3KCA mutant breast: alpelisib
- KRAS G12C: AMG510
Precision Oncology

PROMISE  AND  PITFALLS
Precision Oncology – Pitfalls

• Cost

• Limited benefit

• Test limitations
Precision Oncology – Pitfalls

• Cost

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Pitfalls – Cost

• **Money:** Even with CMS reimbursement and assistance programs, sometimes our patients get stuck with a huge bill.

• **Sample:** For tissue-based assays, you may exhaust a biopsy trying to get testing (which is sometimes still insufficient).

• **Time:** To get the results back, to interpret them, and then to get the appropriate therapy (often off-label or on trial if even available).
Precision Oncology – Pitfalls

• Cost

• **Limited benefit**

• Test limitations
Pitfalls – Limited Benefit

• **Low response rates:** The benefit rate for NGS-based precision oncology trials is consistently in the 10% or less range.

• **However,** these numbers **EXCLUDE** approved precision therapies, and are almost always studying a heavily-pretreated, last-resort population (where any benefit at all is a win).
Pitfalls – Limited Benefit

• Due to reporting bias in publications and advertising, many patients come in with unreasonable expectations about what NGS-based therapy selection is going to do for them.

• Managing expectations is critical. While super-responses can be seen when trying targeted therapy off-label, these are the exception, not the norm.
Pitfalls – Limited Benefit

• **Unable to get drug:** If a potential targeted therapy is identified off-label, it may be hard to get access to the drug (insurance, compassionate use, trial unavailable).

• A consistent finding in precision oncology trials is that, while about a third of patients may be matched to a possible therapy, only about a third of those actually get the drug (as part of the trial, should be easiest).
Pitfalls – Limited Benefit

• **No good drug exists:** There may be no drug that targets the mutation you find (KRAS G12D).

• Alternatively, the drugs that supposedly target the mutation are ineffective (mTOR inhibitors for PIK3CA).
Pitfalls – Limited Benefit

• **Too late in the course:** The patient may be unfit for any therapy at all.

• Patients may be so heavily pretreated that any therapy will be ineffective (generally true of chemotherapy, particularly targeted agents).
Precision Oncology – Pitfalls

• Cost

• Limited benefit

• Test limitations
Pitfalls – Test Limitations

• **Test is no good:** The test you chose may not have tested for what you wanted (wrong sample, not validated for specific alterations, not in the hotspot panel, failed QC, etc).

• It sounds simple, but if your test didn’t test for X, you won’t find X.
Pitfalls – Test Limitations

• **Wrong biomarker:** Missense mutations and copy number amplifications are often not as meaningful as fusion events and truncations.

• Testing for the same thing using different assays may not be validated (PD-L1, TMB).
Pitfalls – Test Limitations

• **False positives:** Clonal hematopoiesis of indeterminate potential (CHIP) yield false positive mutations on liquid biopsy.

• **False negatives:** Sensitivity on liquid biopsy may be insufficient. Sampling error (bad luck) may yield a false negative.
Pitfalls – Test Limitations

• Variants of unknown significance (VUS): As NGS becomes more widely adopted, we are finding more and more mutations which have an unclear effect.

• In 2015, there were ~3,700,000 missense mutations reported, but only ~25,000 that were known to have clinical significance. This disparity is almost certainly worse today.
Pitfalls – Test Limitations

• Unless you have a very good reason, VUS should not be treated as an actionable mutation.

• However, completely ignoring VUS is also wrong. There are lawsuits being brought because patients with BRCA VUS were inappropriately counseled that they had NO genetic risk, when they actually did.
Pitfalls – Test Limitations

• **Hard to interpret:** Most clinicians have no molecular biology background and are unaware that some concurrent alterations may render the recommended treatments pointless.

• Report recommendations are only as good as the algorithm used, which varies from company to company, and changes over time.
Pitfalls – Test Limitations

• Targeting the same alteration with the same drug in different cancers may not yield the same results (BRAF V600E in melanoma vs. colon cancer).

• Due to the rapid evolution of available data, many clinicians may be unaware of newly available drugs and updated indications.
Precision Oncology – Summary

• Precision oncology works with the right target and the right drug.

• The most benefit from precision oncology comes from approved approaches, so keep up to date!

• Being aware of the limitations to this approach is really important.

• This is a lot more complicated than just reading the report summary.
Precision Oncology – Summary

• We know this is really complicated, but we are here to help!

• Contact info
QUESTIONS?