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Proteomics Gives Us the Cancer Traffic Report

In cancer genotyping, genomics provides the blueprint, while proteomics tells us what has been built – so let's integrate them

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Genomics identifies what a tumor may be equipped to do; functional proteomics reveals what it is actually doing. The next step in precision oncology should be to connect the tumor's genetic blueprint to the functional machinery that ultimately determines phenotype, drug response, and resistance.

Here, we examine the arguments for incorporating functional proteomics into oncology diagnostics, and how this multi-omic approach might work in practice.



Kayla Sparks. Credit: Ignite Proteomics

Genomics tells us what a tumor *can* do...

Genomic testing has transformed cancer medicine because it tells us what is written in the tumor's DNA — the mutations, amplifications, deletions, rearrangements, and fusions that can create or enable oncogenic signaling. But DNA is fundamentally an information archive. It tells us what the tumor has the potential to do; it does not necessarily tell us what the tumor is actually doing at the moment we sample it.

There is a substantial biological distance between a DNA alteration and a functional cancer phenotype. A mutation has to be transcribed into RNA, translated into protein, and then incorporated into a complex network of protein-protein interactions, localization events, feedback loops, and post-translational modifications before it produces a biological effect. At each of these levels, regulation can occur.

This is particularly important for signaling proteins. The abundance of a protein is not necessarily equivalent to its activity. A kinase may be abundantly expressed but inactive, while a relatively modest amount of protein may be highly activated through phosphorylation. Similarly, an oncogenic pathway may be activated downstream of the canonical genomic driver through receptor signaling, epigenetic regulation, ligand availability, protein stabilization, or activation of another pathway.

Proteomics tells us what a cancer *is* doing?

Phosphorylation is a particularly important example. Cancer cells do not simply express proteins; they continually modify them to control their activity. Phosphorylation can determine whether a protein is active, where it is localized, what proteins it interacts with, and how long it persists in the cell. These functional states are largely invisible to conventional DNA sequencing.

The reverse is also important. The absence of a canonical mutation does not mean the absence of pathway activity. A tumor may have an activated PI3K/AKT/mTOR pathway, for example, without harboring an obvious activating mutation in one of those genes. Conversely, a tumor may contain a mutation in a pathway but show little evidence that the pathway is functionally dominant.

There are patients whose tumors harbor bona fide pathogenic genomic alterations such as BRAF V600, EGFR exon20 mutations, or c-MET Exon 14 skipping mutations that don't respond to BRAF, EGFR or MET inhibitors. Why? There are patients whose tumors are wild type for these same genes, and yet they respond to these inhibitors. Why?

This distinction is critical to precision medicine.

Genomics essentially asks: "What could this tumor do based on its genetic instructions?"

Functional proteomics asks: "What molecular machinery is actually operating in this tumor?"

That is a very different — and potentially much more clinically actionable — question.



Chip Petricoin. Credit: Ignite Proteomics

The information gap, and its impacts

The consequences of this gap are not merely academic. They can directly affect how we select therapies and interpret treatment response.

A genomic alteration may be classified as actionable because, in other patients or in experimental models, it has been associated with sensitivity to a particular drug. But that does not guarantee that the alteration is the dominant biological driver in an individual patient's tumor. The pathway may be suppressed by feedback mechanisms, overridden by another signaling network, or rendered irrelevant by downstream alterations.

The opposite problem can occur as well. A tumor may lack the mutation that we have historically used as the molecular entry ticket for a particular therapy, yet demonstrate very strong activation of the pathway at the protein level. If we only look at DNA, that patient may never be considered for a therapy that could potentially be relevant.

> *Two patients with ostensibly the same genomic alteration can have dramatically different responses to the same targeted therapy.*

This is one explanation for a phenomenon clinicians encounter repeatedly: two patients with ostensibly the same genomic alteration can have dramatically different responses to the same targeted therapy. Their DNA may look similar, but their tumors are not functionally identical.

The same principle helps explain acquired resistance. A tumor may initially respond because a targeted therapy successfully suppresses its dominant pathway. Under therapeutic pressure, however, the cancer can activate bypass pathways, alter feedback circuitry, change protein abundance, or modify signaling through post-translational mechanisms. The genome may remain relatively stable while the functional state of the tumor changes substantially.

This creates two fundamental problems with a purely genomic approach.

First, we can develop **false confidence** — assuming that because a genomic target is present, the associated therapy must be relevant.

Second, we can create **false negatives** — assuming that because a canonical mutation is absent, the corresponding pathway cannot be therapeutically important.

Neither conclusion necessarily follows from DNA sequencing alone.

Genomics remains indispensable. But if the clinical question is ultimately "What drug is most likely to work in this patient?", then knowing the tumor's genetic potential is only part of the answer. We also need to understand its functional state.

How proteomics fills the gap

Proteins are where the information encoded in DNA becomes biology. They are the molecular machines that execute virtually every process that allows a cancer cell to survive, proliferate, invade, evade the immune system, and respond — or fail to respond — to therapy.

That makes the proteome a fundamentally different layer of information from the genome.

Proteomics can measure the abundance of proteins, but functional proteomics can go considerably further by examining protein activation states, signaling networks, and post-translational modifications. Phosphoproteomics is particularly powerful because phosphorylation is one of the principal mechanisms by which signaling proteins are activated and regulated.

For example, measuring total AKT tells us how much AKT is present. Measuring phosphorylated AKT can provide information about whether

AKT signaling is actually engaged. Looking simultaneously at multiple nodes within the pathway can provide even greater insight: is PI3K signaling active? Is AKT activated? Is mTOR engaged? Are downstream substrates phosphorylated? Is there evidence of feedback activation or compensatory signaling?

That is the difference between measuring a component and measuring a functional signaling system.

Technologies such as reverse-phase protein arrays can be particularly useful for this type of analysis because they allow quantitative measurement of selected proteins and phosphoproteins across large numbers of clinical specimens and signaling pathways using very small amounts of tissue. When coupled with laser-capture or laser-microdissection approaches, measurements can be enriched for tumor cells and reduce the problem of averaging tumor biology together with signals originating from stromal, immune, or normal cells.

This is especially important in heterogeneous tumors. A bulk measurement can tell us that a signal is present somewhere in a specimen without necessarily telling us which cellular compartment is responsible for it.

> *Genomics tells us the blueprint. Proteomics tells us what has been built.*

Functional proteomics answers questions that genomics alone cannot

Genomics tells us the blueprint. Proteomics tells us what has been built, how much of it is present, and — through phosphoproteomic and other functional measurements — what machinery is actually turned on. For example:

- Is the protein encoded by the genomic alteration actually expressed?
- Is it activated?
- Is the expected downstream pathway engaged?
- Is another pathway compensating for it?

- Are there signaling features associated with drug sensitivity or resistance?
- Is the tumor using an alternative biological mechanism that would not have been predicted from its DNA sequence?

Importantly, proteomics does not replace genomics. It completes the picture.

The case for integration

The strongest argument for integrating genomics and proteomics is that they answer different questions.

- Genomics asks: What alterations are encoded in this tumor?
- Proteomics asks: What proteins and signaling pathways are present, active, and functionally dominant?

These are complementary questions, not competing technologies.

Genomics is exceptionally powerful for identifying mutations, gene fusions, copy-number alterations, germline risk, tumor mutational burden, and other established genomic biomarkers. It provides an essential map of the tumor's molecular architecture.

Proteomics adds the next layer: whether that architecture has translated into a functional phenotype.

Imagine finding a genomic alteration in a kinase pathway. The genomic result establishes that the alteration exists. Functional proteomics can then ask whether the kinase and its downstream effectors are actually activated. It may also reveal that a second pathway is simultaneously activated and could provide a mechanism of intrinsic resistance. That additional information can materially change the biological interpretation of the genomic result.

This becomes particularly compelling when the genomic information does not adequately explain the clinical behavior of the tumor.

- Why did a patient with an apparently actionable mutation fail to respond?
- Why did a patient without the expected mutation respond?

- Why did a tumor initially respond and then become resistant?
- Why do two patients with similar genomic profiles behave so differently?

These are fundamentally functional biology questions.

The immediate clinical case for dual profiling is therefore strongest when treatment selection is uncertain, when multiple potentially actionable pathways are present, when genomic findings and clinical behavior are discordant, when resistance has developed, or when a patient is being evaluated for a clinical trial.

> *Precision medicine should mean measuring the information that is most relevant to the clinical decision.*

A new paradigm for precision medicine

It's also worth emphasizing that the goal should not be to create another indiscriminate “test everything” paradigm. Precision medicine should mean measuring the information that is most relevant to the clinical decision.

The larger opportunity is to move from a model of precision oncology based primarily on molecular alterations to one based on molecular alterations plus functional state.

That is a much closer approximation to the biology that determines whether a drug will actually work.

Consider the case of metastatic cancer that has progressed from NCCN guidelines. The oncologist has multiple FDA-approved therapy options with different mechanisms of action to consider at a specific line of therapy. Here, a functional proteomic test would provide a molecular-based rationale to help them decide which amongst these approved therapies would have the highest probability of success.

Complementary genomics and proteomics in practice

Implementation should begin at the time of biopsy or surgery. Tissue is precious, and the assays should be designed together rather than treated as completely independent tests after the fact.

The pathologist would establish the diagnosis, assess tumor content and heterogeneity, and identify representative regions of the specimen. Appropriate sections could then be allocated for histopathology, genomic analysis, and functional proteomic analysis. Where necessary, microdissection could be used to enrich the analysis for tumor cells or specific cellular compartments.

The resulting report should not simply provide two independent lists of findings. The real value comes from integrating the results into a functional molecular model of the tumor.

For example, an integrated report could address:

- **Genomic alterations:** What mutations, amplifications, deletions, or fusions are present?
- **Protein expression:** Are the corresponding proteins actually expressed?
- **Protein activation:** Are the relevant proteins activated, particularly through phosphorylation or other post-translational modifications?
- **Pathway activity:** Are downstream signaling networks functionally engaged?
- **Compensatory signaling:** Are alternative or bypass pathways active?
- **Concordance:** Do the genomic and proteomic results tell the same biological story?
- **Discordance:** If they disagree, what might explain the difference?
- **Therapeutic relevance:** Is there clinical evidence supporting intervention against the identified pathway?
- **Evidence level:** Is the finding clinically validated, supported by prospective evidence, or hypothesis-generating?

Consider a tumor with a genomic alteration involving a particular signaling pathway. Genomics may identify the alteration and suggest a candidate therapy. Proteomics can then determine whether the corresponding protein is expressed and whether the expected downstream pathway is activated. If the pathway is inactive, that may provide an important reason to question whether the genomic alteration

is the dominant therapeutic vulnerability. If the pathway is strongly activated, but a second survival pathway is simultaneously engaged, the proteomic profile may provide a biological explanation for incomplete response or resistance.

Conversely, functional proteomics may reveal robust activation of a pathway for which conventional genomic testing identifies no canonical driver. That observation would not automatically make the pathway a clinically validated therapeutic target — but it could provide a compelling rationale for additional genomic investigation, orthogonal biomarker testing, or enrollment in an appropriate clinical trial.

This distinction is important. Functional proteomics should not be presented as a magic answer or as a replacement for evidence-based clinical decision-making. Rather, it provides a layer of biological information that can make the interpretation of genomic data substantially more meaningful.

In practice, these integrated results could be reviewed by a molecular tumor board that includes pathology, medical oncology, molecular diagnostics, and computational biology expertise. Over time, prospective clinical studies can determine which functional protein and phosphoprotein signatures are sufficiently reproducible and predictive to become validated clinical biomarkers.

Understanding the molecular machinery

The ultimate goal is not to order every possible molecular test on every patient. It is to establish a more biologically complete diagnostic framework.

Cancer is not caused by DNA alone. DNA provides the instructions, but proteins execute those instructions. Drugs overwhelmingly interact with proteins, protein complexes, and the pathways they control — not with an abstract genomic sequence.

If precision oncology is ultimately about matching the right patient to the right therapy, then we need to know not only what mutations a tumor carries, but what molecular machinery is actually operating inside that tumor at the time we make the treatment decision.

Genomics gives us the map.

Functional proteomics gives us the traffic report.

The future of precision oncology should be the integration of both.

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