APPLICATION NOTE

SAPIENT

Predicting Drug-Induced Organ Injury

Ultra-high throughput mass spectrometry that **reads injury signatures in cell culture & translates them to human physiology.**

No safety problem ends more drug programs or forces more market withdrawals than drug-induced organ injury, and liver injury leads the list. **Sapient screens thousands of compounds by nontargeted metabolomics and lipidomics in cells and spent culture media, reads the small molecule signature of injury directly, and then confirms in our DynamiQ™ molecular-clinical database which of those signatures also mark real injury in patients.** The result is an early, translatable readout of human toxicity, the failure mode the industry openly admits it cannot predict.

Toxicity is the reason most drug candidates fail, and injury to the liver is the single largest contributor. Drug-induced liver injury is the most common cause of acute liver failure in developed countries and the most frequent reason a drug is withdrawn from the market or carries a black-box warning. It ends compounds in preclinical development, halts them in the clinic, and forces label restrictions on molecules that are otherwise effective. The same pattern holds for the heart, the kidney, the lung, and the nervous system, where drug-induced injury is hard to anticipate and expensive when discovered late. The financial implications are unforgiving, and a safety failure found in the clinic or after approval costs orders of magnitude more than one found in a screen.

These failures persist because the tools used to screen for injury early do not translate to humans. Animal toxicology misses a large share of human hepatotoxicity, particularly the idiosyncratic injury that appears only in people. *In vitro* screens built on imaging, DNA, or gene expression report changes inside a cell or a model system, but they leave open the question that actually matters, which is whether the same change occurs in a patient and can be seen there. A signal that predicts injury in a dish is only useful if it also marks injury in a person, and most modalities cannot make that connection.

Why Current Screening Modalities Miss Human Injury

Each of the most common modalities used to profile treated cells captures important biological insights, but stop short of a measurement that carries into the patient.

Screening Modality	Limitation for Predicting Human Injury
Cell Painting and High-Content Imaging(IHC)	Predictive *in vitro*, but morphology is not a measurement that can be made in a patient, so an imaging hit cannot be confirmed in human blood.
DNA Sequencing	Describes what a cell could do, not what is actually happening. DNA is static and does not report an active, dynamic injury process.
RNA Sequencing	Works in cultured cells, but transcripts are confined to the intracellular space, so confirming a signal in humans needs tissue that is rarely obtainable.
Proteomics	Excellent for tissue markers and mechanism, but not fast or inexpensive enough to screen thousands of compounds, and most proteins do not circulate at the levels injury screening requires.

Metabolites and lipids are the exception. They are the functional biochemistry of injury itself, changing within minutes to hours of an insult, and they cross cell membranes into the surrounding fluid and then into the blood. The same molecule that marks injury in a culture dish can therefore be measured in a patient's plasma, which is precisely the property that transcripts and most proteins lack.

The Sapient Metabolomic & Lipidomic Approach

Screening Thousands of Compounds in Cells and Media

Sapient runs nontargeted metabolomics and lipidomics on both the cells and the spent culture media from compound-treated cultures, **measuring more than 15,000 small molecule markers in a single run,** including thousands of unannotated features that carry biochemical activity and are blind to DNA, RNA, or protein measures. Assaying the media captures what an injured cell releases and profiling the intracellular pool reads out the functional activity happening inside it, so a treatment is read from both sides at once.

Sapient's proprietary ultra-throughput **rapid LC-MS (rLC-MS) platform can analyze thousands of samples with drug exposures per day,** which is what makes screening thousands of compounds and their full dose responses practical rather than aspirational. Every compound produces a small molecule signature, and the signature, not a single marker, is what separates an injurious mechanism from a benign one.

The Right Molecules to Cross From the Dish to the Patient

Because metabolites and lipids are the downstream, functional output of a cell's biochemistry, they report an active injury process rather than the potential for one. They also move freely across cell and organelle membranes, into the culture media, and into the circulation, which means an **injury signature discovered *in vitro* can be carried intact to human confirmation.** This is the biological basis for translation, and it is the reason a metabolomic and lipidomic screen does not stall at the edge of the dish the way imaging, DNA, and RNA-based screens do.

Translation Through DynamiQ

The screen identifies which compounds injure cells. DynamiQ answers the harder question of which of those signatures are truly specific to human injury. **DynamiQ is Sapient's database of more than 67,000 plasma samples from over 15,000 individuals, profiled on the same metabolomic and lipidomic platform and linked to clinical outcomes across more than 60 diseases,** including hepatic, renal, cardiac, and neurological conditions, with a median follow-up of well over a decade. Because the *in vitro* and *in vivo* measurements are made the same way, an injury signature found in cell culture can be mapped directly onto the plasma signatures of patients with real liver injury.

Signatures that appear in the dish but never in injured patients can be set aside as artifacts of the model system, and signatures that mark injury in both are the ones worth acting on. Sapient's foundation AI model of liver injury, trained on the DynamiQ metabolome, sharpens this further by defining the human injury state against which every candidate signature is scored. Translation, not *in vitro* prediction alone, is the differentiator, because it separates the signals that will hold up in a patient from the ones that will not.

Beyond the Liver: One Platform for Drug-Induced Tissue Injury

Liver injury is the priority because it drives the most attrition, but the same platform reads injury wherever it occurs. Cardiotoxicity, another leading safety-driven cause of drug withdrawal, produces distinct lipid and metabolite changes as cardiac cells are stressed.

Drug-induced kidney injury, lung injury, and peripheral and central neurotoxicity each leave their own biochemical fingerprint in cells, media, and circulation, and **each can be screened in vitro and confirmed against the matched human signatures in DynamiQ.** Skeletal-muscle injury, pancreatic and metabolic toxicity, and hematologic effects extend the same approach. Because the readout is a broad, untargeted signature rather than a fixed panel, a single screen can flag injury across multiple organ systems at once, including off-target toxicities a program did not know to look for.

De-Risking Safety Across Development

Historically, teams have screened for toxicity with assays that predict events in a model system and hoped the prediction would hold in people. Sapient **reframes the question from what changes in a dish to what change also marks injury in a patient, and answers it early,** when it is still a chemistry or candidate-selection decision rather than a clinical failure. This is particularly valuable when a team is asking:

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To start a **screening collaboration or a translational safety program,** contact **discover@sapient.bio**.

Development Question	Sapient Insight
Which of our compounds carry a liver-injury liability, and at what dose?	Nontargeted metabolomic and lipidomic screening of cells and media ranks the full series by injury signature and dose response.
Is this *in vitro* signal real in humans?	Direct mapping of the *in vitro* signature onto plasma signatures of injured patients in DynamiQ, scored against a foundation model of human liver injury.
Does the toxicity extend beyond the liver?	A single untargeted readout flags cardiac, renal, pulmonary, neuropathic, and other tissue-injury signatures at the same time.
What is the mechanism of injury?	Pathway-level changes across the metabolome and lipidome point to the biochemistry driving the toxicity, not just its presence.
Can we monitor this liability into the clinic?	The same circulating signature transfers to a plasma assay for pharmacodynamic and safety monitoring in patients.