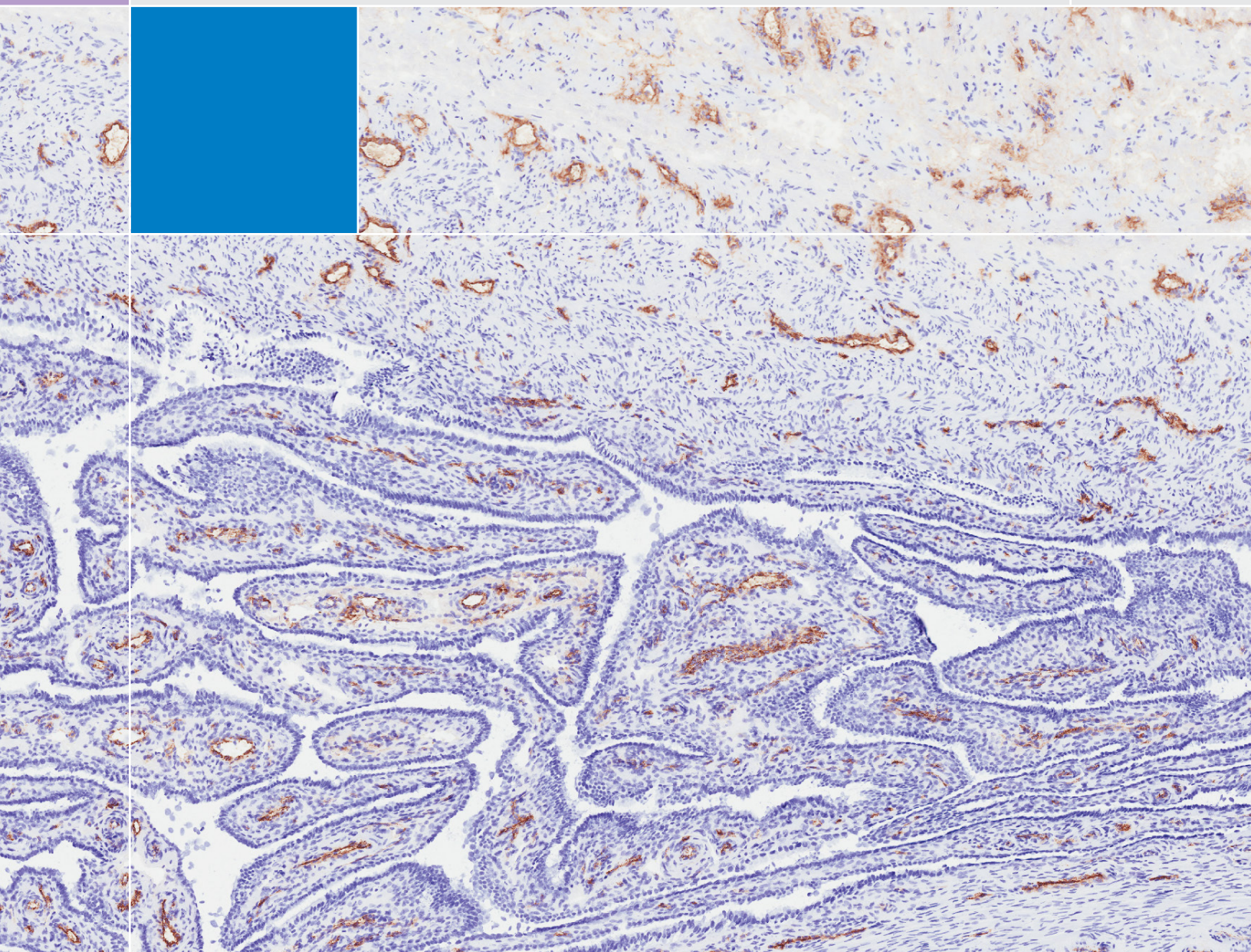
PRECISION for medicine®

GLP Tissue Cross Reactivity Testing

Your Needs, Our Expertise



Tailored Methodology for Biotherapeutic Safety Studies

Precision for Medicine's unique combination of research services and tissue procurement capabilities form the pillars of our GLP Tissue Cross Reactivity (TCR) Services.

Precision for Medicine is a leading supplier of well-characterized biospecimens for research—all collected through a global network of healthcare specialists. All human tissues recommended for TCR testing by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are fully consented for commercial research, and available from at least 3 male and 3 female donors.

Clients may elect to have their TCR studies conducted in compliance with Good Laboratory Practice (GLP) or under non-GLP conditions. For TCR studies, our service provides clients with an accurate assessment of the on- and off-target binding of their therapeutic antibody candidates, or related products, in human tissues. Our expertise in IHC assay development, combined with a tailored scientific approach, enables us to deliver high-quality data to our clients in a defined time to accelerate the development of their therapeutic antibody candidate programs.

Key Benefits:

- Established inventory of the 36 human tissue types required, providing a quick turnaround for your study without delays sourcing scarce tissues
- Robust qualification of tissues from procurement to assay use, resulting in superior data quality and reduced time lost due to experimental failure
- Expert assay optimization, providing confidence in the scientific integrity of the results
- Flexible study design: either non-GLP tissue microarray (TMA) screening to provide an initial assessment or GLP study using full-face sections
- Fully automated immunohistochemical (IHC) assays, offering consistent and reproducible results
- State-of-the-art MHRA-certified, GLP-compliant facility
- Experienced scientific and pathology staff, resulting in delivery of even the most technically challenging assays

Tissue Types Are Available From Multiple Male and Female Donors		
Adrenal gland	Ileum	Prostate
Bladder	Kidney - glomerulus and tubule	Skeletal muscle
Blood cells	Liver	Skin
Blood vessel endothelium	Lung - bronchus and parenchyma	Spinal cord
Bone marrow	Lymph node	Spleen
Breast	Ovary	Stomach
Cerebellum	Pancreas	Testis
Cerebral cortex	Parathyroid gland	Thymus
Colon	Parotid salivary gland	Thyroid gland
Eye	Peripheral nerve	Tonsil
Fallopian tube	Pituitary gland	Ureter
Heart	Placenta	Uterus - cervix and endometrium

Please contact us regarding availability of other tissues.

Complete, Comprehensive, Compliant GLP TCR Services

Guidelines issued by the FDA and EMA for the development of therapeutic antibodies and related products recommend their testing for TCR on a range of human tissues.[1,2] Given that such testing is performed in the pre-clinical phase of drug development prior to submission of Investigation New Drug (IND) applications to the FDA in the United States or Regulatory Authorities elsewhere, it is recommended that the data are generated to GLP.

Precision for Medicine's scientific team provides a customized service to meet your specific requirements for your biotherapeutic agent. We utilize a 2- or 3-phase approach that provides a cost-effective solution for making confident decisions regarding the best parameters for your study and minimizes the risk of GLP study failure. We deliver a final report that is suitable for submission as part of an IND application to the FDA or other Regulatory Authorities.

Meticulously Qualified Specimens for Your TCR Studies

Each of our TCR studies begins with well-characterized human specimens that have been rigorously qualified to meet the exacting requirements of this research.

Our specimens undergo a 4-point inspection to qualify for GLP TCR studies:

1. Donor clinical history evaluation to ensure experimental suitability
2. Specimen review by board certified pathologists to validate normal morphology
3. Confirmation of compliance with ethical, legal, and regulatory requirements
4. Initial confirmation of tissue antigenicity

Confirmation of Tissue Antigenicity

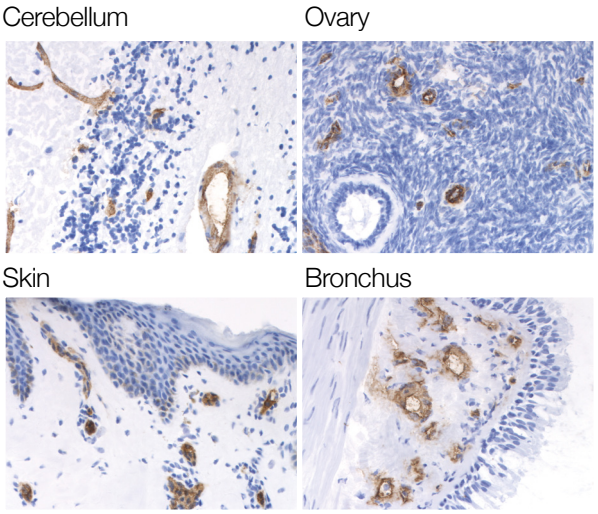


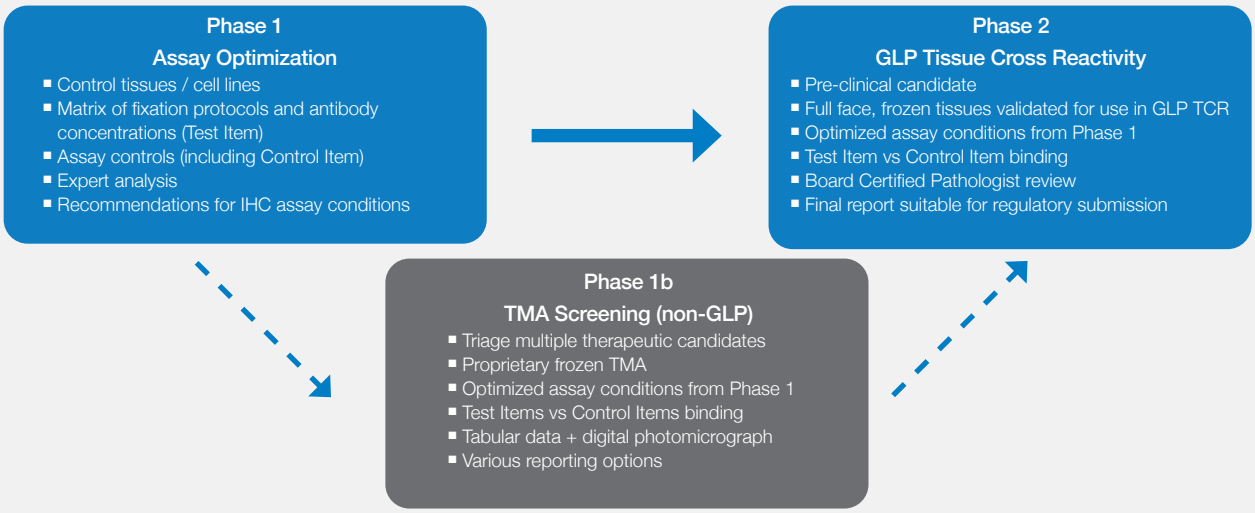
Figure 1. Confirmatory assays are performed to validate the antigenicity of tissues used in TCR studies. One such test involves the immunostaining of tissues with von Willebrand Factor (vWF) antibodies. Images show the binding of vWF antibodies to the microvascular endothelium proteins in frozen sections of cerebellum, ovary, skin, and bronchus.

References

1. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, Docket No. 94d-0259. February 28, 1997.

2. Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products, EMEA/CHMP/BWP/157653/2007. Adopted December 18, 2008.

Our 3-Phase Approach Provides Quality Data for Your Study



Phase 1 Assay Optimization Data

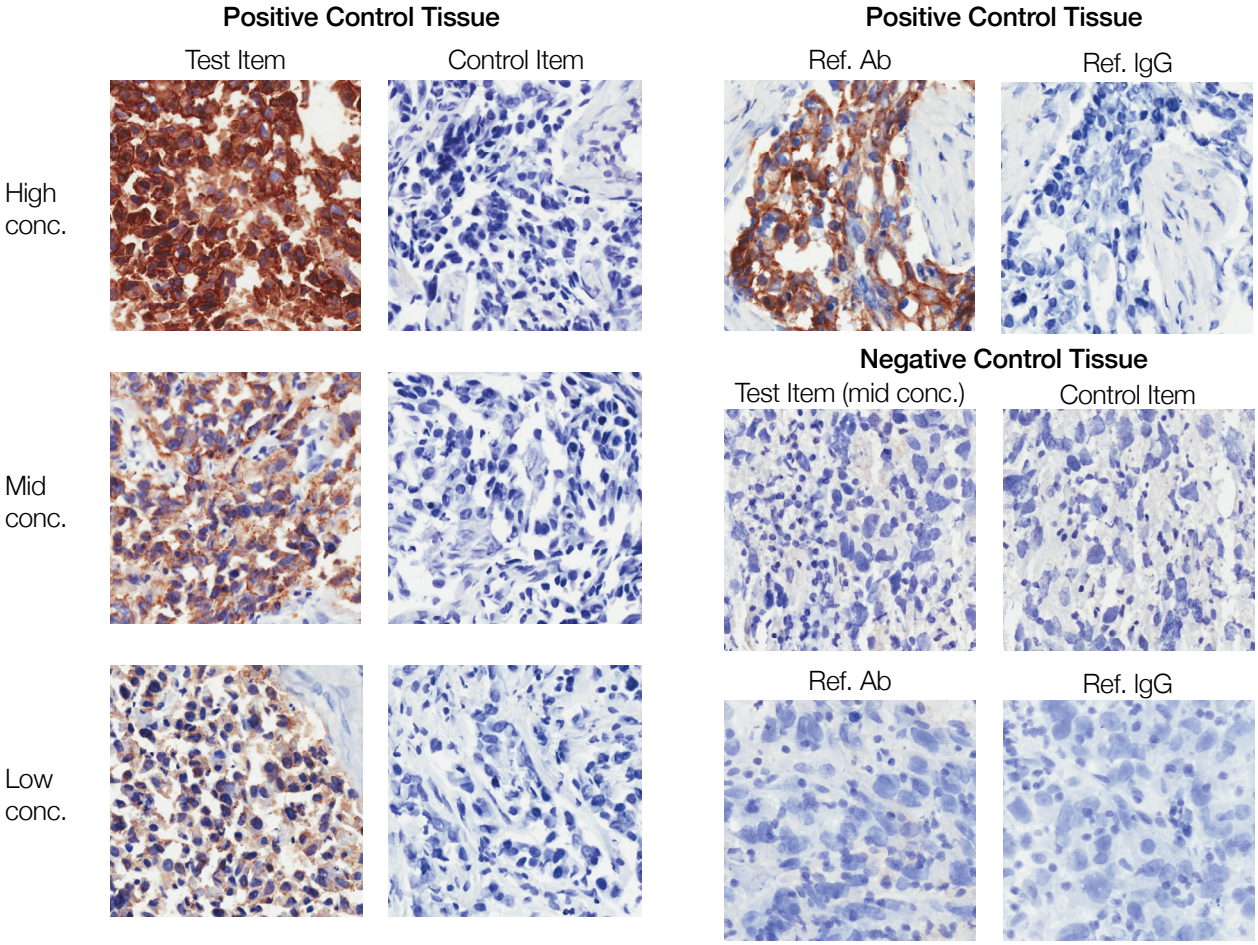


Figure 2. Left-hand panels show frozen sections of positive control tissue incubated with 3 concentrations of Test Item and Control Item. The panels demonstrate specific, concentration-depending Test Item binding. Binding of a reference antibody (same target - Ref. Ab.) and an equivalent concentration of non-immune IgG are shown for comparison. The pattern of binding appears quantitatively similar. No binding of either the Test Item nor the reference antibody was observed in the negative control tissue.

Phase 2 GLP TCR Data

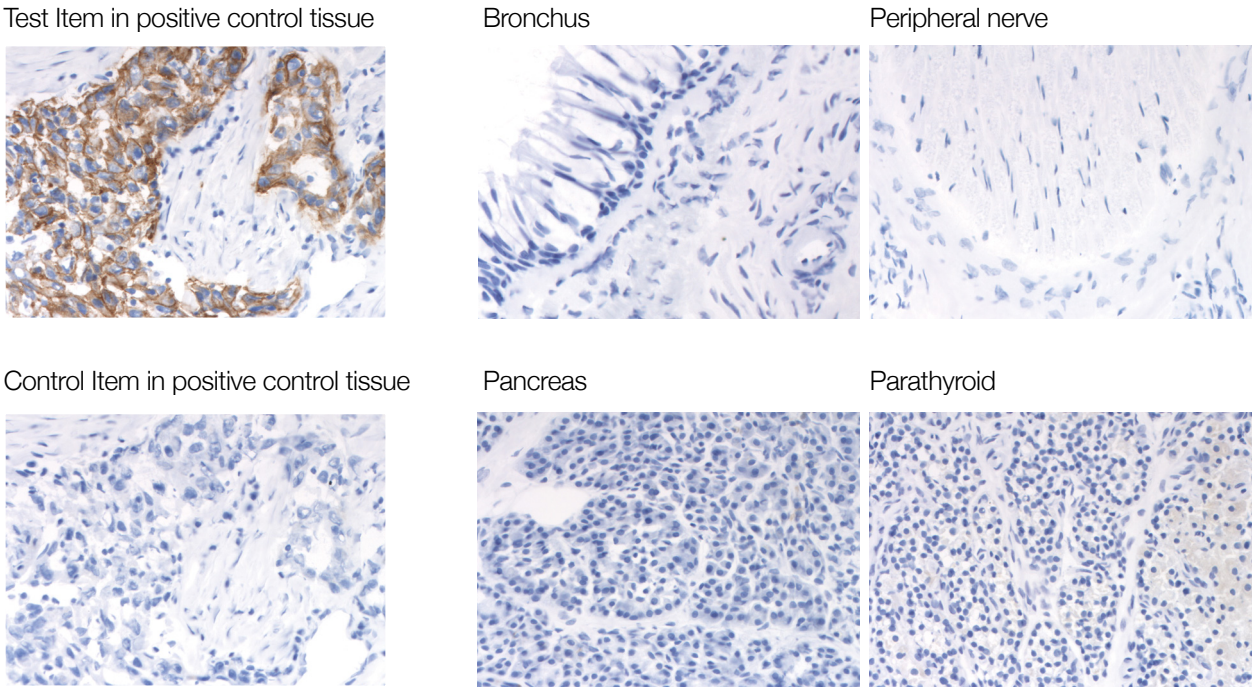


Figure 3. The left-hand panels show the optimized IHC assay binding of Test Item and Control Item to the positive control tissue. The right-hand panels show absence of Test Item binding to cryosections of bronchus, peripheral nerve, pancreas, and parathyroid.

Phase 1b Frozen Tissue Microarray Screening

Swift, Accurate Detection

TCR screening using frozen TMAs offers a non-GLP option as an economical alternative to full face sections for a rapid turnaround on screening candidate molecules.

Our scientists have developed a panel of TMAs containing the 36 tissues required by the FDA and EMA for assessment of therapeutic antibody candidates. Utilization of this approach is designed to accelerate the de-selection of antibody candidates that exhibit significant “off-target” immunoreactive profiles.

Advantages of this service include:

- Assessment of all 36 FDA and EMA tissues; provides actionable feedback on “off-target” effects that can be incorporated into early antibody evaluations
- Single assay format; provides economical alternative to full face sections
- Experiments performed with the same experts, tissues, and IHC methods employed for our GLP studies; provides confidence in the results

Frozen TMA for TCR screening

Figure 4a. Frozen, normal tissue TMA for TCR screening.

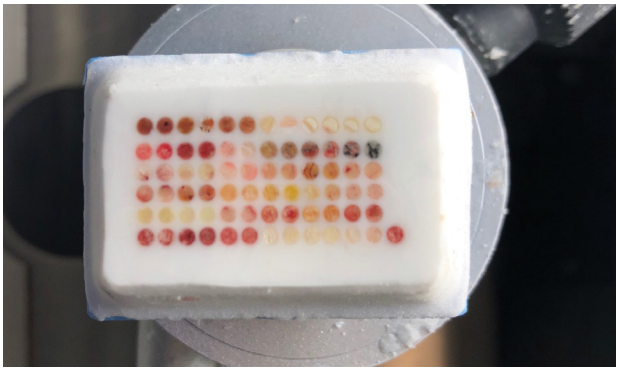
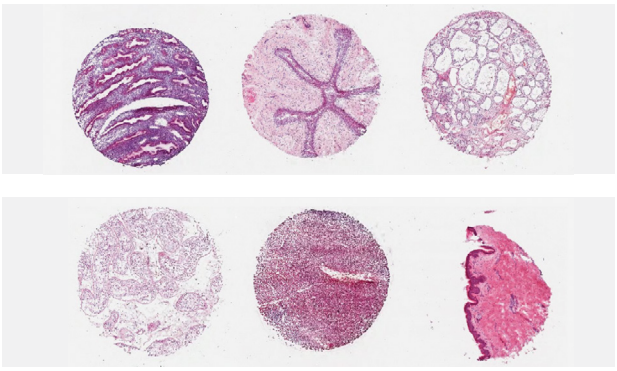


Figure 4b. H&E images of selected cores from our frozen TMA.



Top left to bottom right: uterus endometrium, ureter, thyroid, testis, spleen, and skin

Quality Construction

- Three-array set—each block containing 12 tissues from 3 donors each, in duplicate
- Tissue selection using the same parameters as our GLP level studies
- Pathology review to ensure all cores are representative of the full tissue section
- Tissue remains frozen throughout the coring and TMA construction process

Excellent Results

- Tabulated data with secure online access to Aperio scanned images—suitible to identify "off-target" effects
- Reporting options available

Precision for Medicine has made a significant investment to create a state-of-the-art facility and quality management system for providing GLP-compliant immunohistochemical studies. Precision for Medicine has been a full member of the Medicines and Healthcare Products Regulatory Agency (MHRA) UK GLP Compliance Monitoring Programme since February 2010, with a track record of successful inspections by the MHRA. These resources allow us to provide our clients with efficient delivery of high-quality data to support their IND submission.

Scientific Expertise Paving the Way to Personalized Medicine

Precision delivers specialized strategic and scientific services, infrastructure, and technologies to help life science organizations develop and commercialize individualized medicines and targeted therapies that can change patient outcomes. We are committed to partnering with our customers to accelerate development and support commercialization through personalized medicine. Listed below is a high-level summary of our Bioservices offerings.

Sample Protection

Logistics

- Site support and lab manuals
- Custom kitting
- Transport management
- Processing
- Processing of any fluid or tissue type
- Strategically created lab infrastructure to enable global real-time processing with uniform quality

Specimen Inventories

- Online tracking and reporting
- Master virtual sample inventories across Precision and external labs leveraging Precision-developed technology-enabled infrastructure (QuartzBio℠)
- Dynamic reporting and actionable dashboards

Storage

- 77,000 square foot facility
- Storage of all tissue types and temperatures
- World-class quality standards and certifications (CAP, ISO, GxP)

Data Management

Precision-developed technology-enabled infrastructure for integrating and delivering all specialty marker data (QuartzBio℠)

- Secure, web-based user interface for interactive ‘omics data exploration and knowledge generation with integrated on-the-fly analytics and reporting
- Purpose-built ‘omic data integration capability for data generated within Precision, clinical data, as well as data generated in external labs
- Efficient trial submission formats

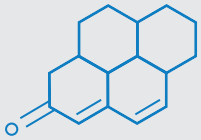
Comprehensive solutions for analyzing all specialty marker data

- Standard statistical analysis for biomarker data
- Advanced computational biology and AI-driven analytics capabilities for translational research

DX Development

- Regulatory strategy, submissions, and negotiations
- Clinical trial solutions, including protocol development, including site identification, site qualification, study management, monitoring, and data management

Biomaterials and Sample Sourcing



- PBMCs and highly purified PBMC subsets
- FFPE and tissue capabilities
- Healthy and disease state leukopaks
- Biorepository of biofluid specimens
- Prospective collections

Design and Execution

Clinical Immune Monitoring

- Scientifically driven and globally scalable
- Standard panels and custom assay development / validation
- ICS, phospho-flow, cell-surface, and soluble markers
- Redundancy across labs for flow, ELISpot, ELISA
- DNA / RNA profiling and expression using Nanostring

Custom Cell-Based Assays

- Measurement of level or function of any cell type
- Assay development using primary cells or cell lines
- Examples include: T cell activation / proliferation, MLR, ADCC/CDC, NK cell assays, dendritic cell assays, multiplex cytokine profiling

Bioanalytical Services for Large Molecules

- Biomarker strategy
- Globally renowned expertise in immunogenicity (ie, anti-drug antibody and neutralizing antibody assays) and PK
- Further specialty in unique assays, eg, anti-PEG, IgE response, complement activation, gene therapies, and complex biologics (eg, ADC, Bispecifics)

qPCR-Based/Epigenetic Assays

- Identification and quantification of specific immune cell types using qPCR-based, epigenetic assays

Tissue and Liquid Biopsy Profiling

- IHC and pathology services including custom assay development, validation, and real-time clinical trial enrollment testing
- Quantitative Immunofluorescent Analysis on tissues and cells
- ApoStream®, a proprietary rare cell enrichment platform optimized for enrichment of CTCs for downstream analysis
- NGS capabilities with optimized protocols to drive sensitivity of detection (WES, RNASeq, etc)

Discover the Precision difference. Consult with our experts about your situation and needs. Once you've experienced our thinking, you'll understand the Precision difference. To set up an appointment or to learn more, email us at **info@precisionformedicine.com,** call us at **+1 855.222.5010**, or visit **precisionformedicine.com/contact.**

Notes

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