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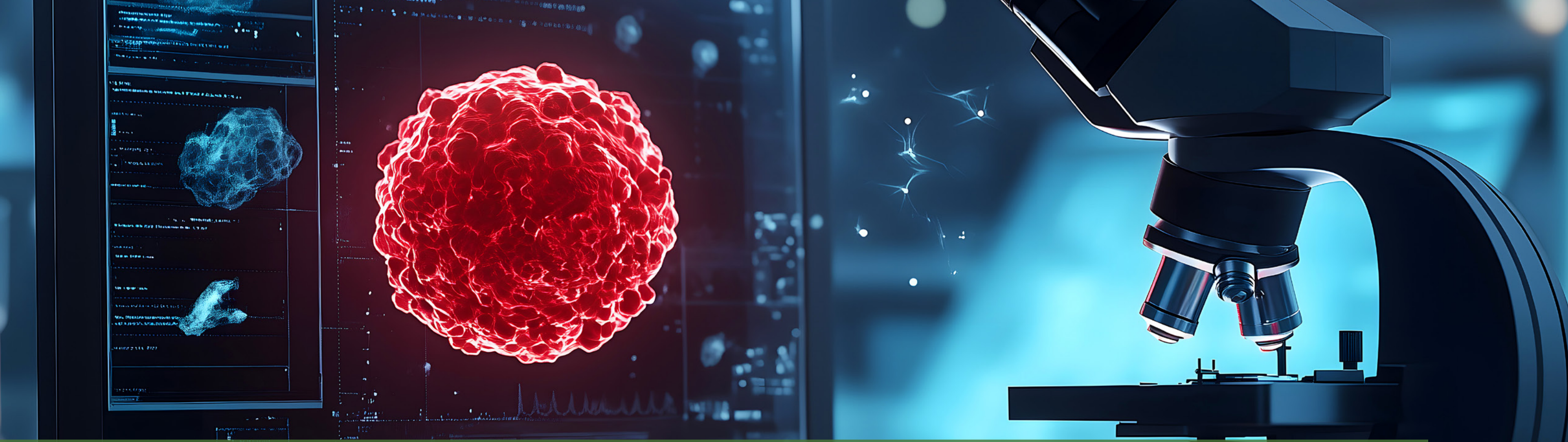
BioPharma Services | Oncology

ANTIBODY-DRUG CONJUGATES

Precision therapeutics powered by diagnostic innovation



Introduction

The ADC revolution

Antibody-drug conjugates (ADCs) are at the forefront of precision oncology, offering a unique therapeutic approach that combines the specificity of targeted therapies with the potency of traditional chemotherapies. These sophisticated drugs have ushered in a new era of cancer treatment by addressing one of oncology's greatest challenges: delivering cytotoxic agents directly to cancer cells while minimizing damage to healthy tissue.

The recent surge in ADC development and approvals reflects their growing importance in the fight against cancer. With over 180 ADCs in clinical pipelines and an increasing number of FDA approvals, the pharmaceutical industry has embraced this technology, leading to significant mergers, acquisitions, and investment activity. In 2022 and 2023 alone, there were over 140 ADC-related transactions announced, valued at more than $140 billion. This momentum highlights not only the therapeutic promise of ADCs but also the challenges associated with their development, which require precision at every step—from selecting the right target to ensuring safe and effective delivery.

Testing plays a pivotal role in the success of ADCs. Diagnostic tools are essential for identifying suitable targets, optimizing patient selection, and ensuring that these therapies are both safe and effective. As ADCs evolve to target more complex biomarkers, the need for robust, innovative diagnostics has never been greater. Companion diagnostics (CDx), in particular, are becoming increasingly central to ADC development, as pharmaceutical companies explore novel antigens, including tumor-specific antigens (TSAs) and neoantigens, that require precise validation and patient stratification.

In this paper, we will explore the science behind ADCs, the critical role of testing in their development and use, and the key capabilities that define an ideal diagnostic partner. We will also highlight how Quest Diagnostics, through its specialized PhenoPath Laboratories division, provides end-to-end support for ADC development—from preclinical assay design to nationwide clinical deployment. Together, Quest and PhenoPath are uniquely positioned to support pharmaceutical companies in advancing the next generation of ADCs.

[1]Alira Health. (2024). 2024 global antibody-drug conjugates (ADC) report. Retrieved December 12, 2024, from https://alirahealth.com/education-hub/2024-global-antibody-drug-conjugates-adc-report

[2]Oncology Pipeline. (n.d.). How hot are antibody-drug conjugates? Retrieved December 12, 2024, from https://www.oncologypipeline.com/apexonco/how-hot-are-antibody-drug-conjugates

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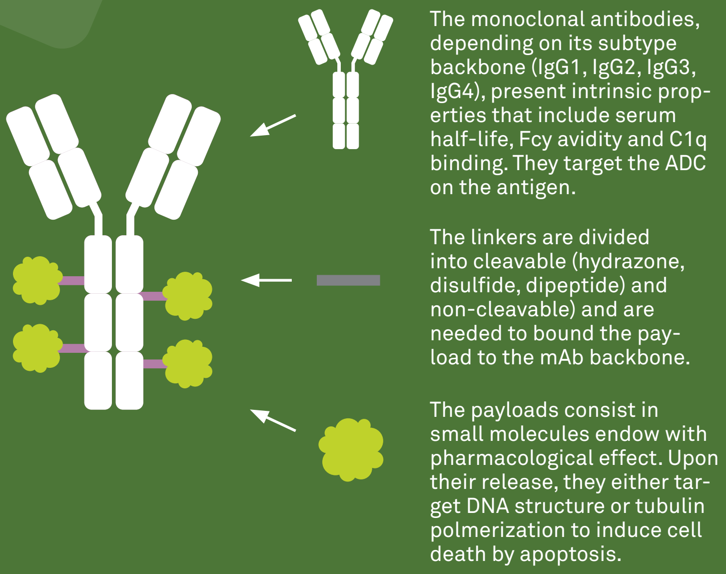
What is an antibody-drug conjugate (ADC)?

ADCs are a class of biopharmaceuticals that represent the next frontier in targeted cancer therapy. By combining the precision of monoclonal antibodies (mAbs) with the potency of cytotoxic drugs, ADCs offer a unique mechanism for selectively targeting cancer cells while sparing healthy tissue.



The modular components of an ADC and their roles in targeted cancer therapy.

How ADCs work

Antibody-drug conjugates are highly sophisticated therapies that operate through a modular design, combining 3 key components: a monoclonal antibody, a linker, and a cytotoxic payload. This intricate structure enables ADCs to deliver potent treatments directly to cancer cells with minimal impact on healthy tissues.

1. **Monoclonal antibody (mAb):** At the core of every ADC is a monoclonal antibody that serves as the targeting mechanism. These antibodies are engineered to recognize and bind to specific antigens expressed on the surface of cancer cells. The precision of the mAb is critical; it ensures that the ADC selectively attaches to tumor cells while avoiding healthy tissues. Depending on its subtype (eg, IgG1, IgG2), the antibody can influence properties such as serum half-life, immune effector function, and overall stability within the bloodstream. By leveraging the specificity of monoclonal antibodies, ADCs overcome one of the greatest challenges in oncology: delivering treatment precisely where it is needed while sparing healthy cells.

2. **Linker:** The linker is the bridge that connects the cytotoxic payload to the monoclonal antibody. It plays a crucial role in ensuring that the payload remains stable in circulation but is released precisely within the target cancer cells. Linkers can be designed to be cleavable or non-cleavable, depending on the desired mechanism of action. Cleavable linkers rely on environmental triggers, such as pH changes in the acidic lysosome, to release the payload once inside the tumor cell. Non-cleavable linkers, on the other hand, require the entire ADC to be metabolized within the cell for the payload to take effect. Advances in linker technology have significantly improved the stability and efficacy of ADCs, reducing off-target toxicity and ensuring greater therapeutic precision.

3. **Cytotoxic payload:** The payload is the “weapon” within the ADC, designed to kill cancer cells once delivered. These cytotoxic agents are far more potent than traditional chemotherapies, as they are intended to act in minute quantities. Common payload mechanisms include disrupting tubulin polymerization to prevent cell division or causing direct DNA damage to induce apoptosis. The potency of these agents is what makes ADCs uniquely effective in treating cancers, even when target antigen expression is low. However, this potency also underscores the importance of precise delivery, as systemic exposure to the payload could cause significant harm.

Together, these 3 components form a unified system designed to target, internalize, and destroy cancer cells.

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Step-by-step mechanism

The mechanism of ADC action unfolds through a precise series of steps

1 Targeting and binding

The monoclonal antibody component identifies and binds to its specific antigen expressed on the cancer cell surface. This step is the critical starting point that determines the ADC's selectivity.

2 Internalization

After binding to the target antigen, the ADC is internalized into the cancer cell through receptor-mediated endocytosis. This process draws the ADC into the cell, encapsulating it within an endosome.

3 Payload release

Once inside the cell, the acidic environment of the lysosome triggers the cleavage of a cleavable linker or the degradation of a non-cleavable linker. This action releases the cytotoxic payload from the antibody, activating its therapeutic effects.

4 Cancer cell destruction

The released payload exerts its lethal effect, either by disrupting essential cellular functions such as mitosis or by causing irreparable DNA damage. The result is the targeted destruction of the cancer cell while sparing surrounding healthy tissue.

This stepwise approach enables ADCs to harness the potency of traditional cytotoxic agents while addressing the precision challenges of modern oncology. The modularity of ADCs also allows for continuous optimization, with advancements in each component improving their efficacy, safety, and clinical application.

The evolution of antibody-drug conjugates

The journey of antibody-drug conjugates (ADCs) from conceptual innovation to therapeutic option has been marked by both challenges and triumphs. When ADCs first entered the oncology landscape, the promise was clear, selectively delivering cytotoxic agents directly to cancer cells, sparing healthy tissues and reducing systemic toxicity. However, early iterations faced significant limitations that tempered their success. The first FDA-approved ADC, Mylotarg™ (gemtuzumab ozogamicin), highlighted both the promise and perils of the technology. Approved in 2000 for acute myeloid leukemia, Mylotarg™ suffered from unstable linkers and off-target toxicity, which led to its voluntary withdrawal in 2010. Despite its reapproval in 2017 with a refined dosing strategy, it underscored the need for innovation across all aspects of ADC design.[3]

Over the years, a series of technological breakthroughs elevated ADCs from a challenging concept to one of the most promising therapeutic classes in precision oncology. Advances in linker technology addressed early concerns of instability, with modern linkers designed to remain intact during systemic circulation and release the payload precisely within cancer cells. At the same time, cytotoxic payloads evolved to include highly potent agents capable of overcoming low antigen expression on tumor cells. These developments, combined with improved antibody engineering to minimize immunogenicity and optimize pharmacokinetics, resolved many of the issues that had hindered ADCs in their early days. The result was a new generation of ADCs that could reliably target cancer cells while sparing healthy tissue.

The past decade has seen ADCs enter a golden era of development, driven by these advancements. Between 2011 and 2024, the FDA approved a wave of ADCs, including Kadcyla®, Adcetris®, and Enhertu®, each demonstrating the potential of this therapeutic class to address unmet needs in oncology. This recent activity reflects not only improvements in ADC design but also a deeper understanding of patient selection. The integration of companion diagnostics into clinical development now allows pharmaceutica companies to identify patient populations most likely to benefit from ADC therapy.[3]

The evolution of ADCs is perhaps best illustrated by the state of recent FDA approvals, which demonstrates their growing importance in oncology. A table of FDA-approved ADCs (see below) highlights this trajectory, showing a clear acceleration in approvals and expanding indications. This activity aligns with an even larger pipeline, underscoring the industry's confidence in the future of this technology.

[3] Nawrat A. Timeline: charting the choppy history of 'magic bullet' antibody-drug conjugates. Pharmaceutical Technology website. Published February 1 0, 2021. Accessed December 12, 2024. https:// www. pharmaceutica 1-technology.com/features/antibody-drugconjugates-timeline/

Brand	Generic Name	Company	Indication(s)	Approval Date	Antigen	Antibody	Linker	Cytotoxin	CDx
Mylotarg	gemtuzumab ozogamicin	Pfizer	Acute Myeloid Leukemia (AML)	05/17/2000-2010; 09/01/2017	CD33	Humanized IgG5 mAb	hydrazone linker	calicheamicin	
Adcetris	brentuximab vedotin	Seattle Genetics	Relapsed or Refractory CD30+ Hodgkin Lymphoma (HL), Systemic Anaplastic Large Cell Lymphoma (sALCL)	08/19/2011	CD30	Chimeric IgG1 mAb	protease-cleavable valine-citruline linker	Monomethyl Auristatin E (MMAE)	
Kadcyla	trastuzumab emtansine	Genentech (Roche)	Metastatic HER2-Positive Breast Cancer; Adjuvant treatment of HER2-positive early breast cancer	02/22/2013; 05/032019	HER2	Humanized IgG1 mAb (trastuzumab)	Non-cleavable linker	DM1	HER2 expression
Besponsa	inotuzumab ozogamicin	Pfizer	Adults with Relapsed or Refractory CD22-Positive B-Cell Precursor Acute Lymphoblastic Leukemia (ALL); Pediatric Patients Aged 1 Year and Older with Relapsed or Refractory CD22-Positive B-Cell Precursor	08/17/2017; 03/06/2024	CD22	Humanized IgG4 kappa mAb	Acid-cleavable linker	N-acetyl-gamma-calicheamicin	
Lumoxiti	moxetumomab pasudotox-tdfk	AstraZeneca	Adult Patients with Relapsed or Refractory Hairy Cell Leukemia (HCL)	09/13/2018	CD22	Recombinant murine mAb (moxetumomab)	Peptide linker	Pseudomonas exotoxin A	
Polivy	polatuzumab vedotin-piiq	Genentech (Roche)	Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL); Previously Untreated Diffuse Large B-Cell Lymphoma (DLBCL)	06/10/2019; 04/19/2023	CD79b	Humanized IgG1 kappa mAb	protease-cleavable valine-citruline linker	Monomethyl Auristatin E (MMAE)	
Padcev	enfortumab vedotin	Seattle Genetics and	Locally Advanced or Metastatic Urothelial Cancer; For use in combination with pembrolizumab as first-line treatment	12/18/2019; 04/03/2023	Nectin-4	Fully Human IgG1 Kappa mAb	protease-cleavable valine-citruline linker	Monomethyl Auristatin E (MMAE)	
Enhertu	trastuzumab deruxtecan	AstraZeneca and Daiichi Sankyo	Unresectable or Metastatic HER2-Positive Breast Cancer; Locally Advanced or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma; Unresectable or Metastatic HER2-Low Breast Cancer; Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer (NSCLC); Unresectable or Metastatic HER2-Positive Solid Tumors	12/20/2019; 01/15/2021; 08/06/2022; 08/12/2022; 04/05/2024	HER2	Humanized IgG1 mAb (trastuzumab)	Tetrapeptide-based cleavable linker	Deruxtecan (DXd)	HER2 expression
Trodelvy	sacituzumab govitecan-hziy	Immunomedics	Triple Negative Breast Cancer (TNBC); HR-Positive, HER2-Negative Breast Cancer	04/22/2020; 02/03/2023	Trop-2	Humanized IgG1 kappa mAb	Proprietary hydrolyzable CL2A	SN-38	
Blenrep	belantamab mafodotin-blmf	GSK	Relapsed or Refractory Multiple Myeloma	08/05/2020-11/2022	BCMA	Humanized IgG1 kappa mAb	Maleimidocaproyl linker (non-cleavable)	Monomethyl Auristatin F	
Zynlonta	loncastuximab tesirine-lypl	ADC Therapeutics	Relapsed or Refractory Large B-Cell Lymphoma	04/23/2021	CD19	Humanized IgG1 kappa mAb	Protease-cleavable valine-alanine linker	Pyrrolobenzodiazepine (PBD) dimer	
Tivdak	tisotumab vedotin-tftv	Seagen Inc. (Pfizer)	Recurrent or Metastatic Cervical Cancer	09/20/2021	Tissue Factor (TF)	Humanized IgG1 kappa mAb	protease-cleavable valine-citruline linker	Monomethyl Auristatin E (MMAE)	
Elahere	mirvetuximab soravtansine-gynx	ImmunoGen, Inc.	Folate Receptor-Alpha (FRa) Positive, Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	11/14/2022	FRa	Humanized IgG1 kappa mAb	Cleavable disulfide linker	DM4 (a Maytansine derivative)	FRa expression

Sources: U.S. Food and Drug Administration. (n.d.). Drugs@FDA: FDA-approved drug products. Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm; National Cancer Institute. (n.d.). Drug dictionary. Retrieved from https://www.cancer.gov/about-cancer/treatment/drugs;European Medicines Agency. (n.d.). Human medicines highlights. Retrieved from https://www.ema.europa.eu/; ClinicalTrials.gov. (n.d.). Clinical trial database. National Institutes of Health. Retrieved from https://clinicaltrials.gov/

The role of diagnostic testing

Diagnostic testing is at the heart of antibody-drug conjugate development, ensuring these precision therapies achieve their full potential.

From identifying suitable targets during research to guiding patient selection in clinical practice, testing underpins every stage of the ADC journey. As ADCs continue to evolve, diagnostic innovation becomes ever more critical, enabling breakthroughs in therapeutic design, regulatory approval, and real-world application.

In the early phases of ADC development, diagnostic testing focuses on validating antigens that can serve as effective therapeutic targets. Clinical trial assays (CTAs) are critical in this stage, assessing the presence and accessibility of target antigens on tumor cells while ensuring minimal expression in healthy tissues. Advances in proteomic and genomic profiling have expanded the universe of potential antigen targets, particularly tumor-specific antigens and neoantigens. These uniquely expressed antigens hold the promise of increasing ADC efficacy and precision, but they also demand sophisticated testing to confirm their clinical relevance. CTAs provide this foundation, offering the data necessary to refine therapeutic candidates and design robust assays that can transition into regulatory submissions and beyond.

As ADCs move from development into clinical trials, the need for precision grows. Companion diagnostics (CDx) play a pivotal role in this phase, ensuring therapies are matched to the patients most likely to benefit. By confirming target antigen expression in tumor tissue, CDx not only optimize patient selection but also align with regulatory requirements for therapies where efficacy depends on antigen presence. With ADCs increasingly targeting complex or variable biomarkers, such as TSAs and neoantigens, the role of CDx is expected to grow significantly in the coming years. These diagnostics can provide supportive data for treatment decisions that are personalized and may result in better outcomes for patients.

Once an ADC reaches the clinic, diagnostic testing continues to play a vital role to help assess safety and effective application. Routine clinical testing confirms antigen expression, monitors patient response, and assesses potential side effects, providing critical insights that inform ongoing treatment decisions. The reliability and scalability of these tests are essential for integrating ADCs into standard oncology care, particularly as their use expands across indications and patient populations.

From CTAs that validate the earliest therapeutic concepts to, CDx that guide precision treatment, and clinical testing that ensures safe application, diagnostics are central to the success of ADCs. As the field evolves, innovative testing methods will remain indispensable, driving progress in therapeutic design and delivering on the promise of precision oncology.

Key capabilities required from a diagnostic partner

The development and commercialization of antibody-drug conjugates require a diagnostic partner with expertise that spans the entire therapeutic lifecycle. From early-stage research to regulatory submission and clinical deployment, the right partner ensures that every diagnostic step aligns seamlessly with the unique demands of ADCs.

Selecting a partner with these capabilities is not merely a convenience—it's a strategic imperative for companies developing ADCs.

Key capabilities include:

- **Deep scientific expertise**

  A diagnostic partner must possess advanced knowledge in technologies such as immunohistochemistry (IHC), next-generation sequencing (NGS), and proteomics, ensuring precision in antigen validation and assay design. This expertise is critical for identifying and validating complex targets like tumor-specific antigens (TSAs) and neoantigens.

- **Regulatory proficiency**

  The ability to navigate complex regulatory pathways is essential, particularly for companion diagnostics, where submission quality can influence FDA approval timelines. A skilled partner ensures seamless codevelopment of ADCs and their associated diagnostics.

- **Scalable infrastructure**

  A partner must deliver consistent, high-quality testing across preclinical, clinical, and commercial settings, ensuring reliability at scale. This capability is especially important as ADC therapies transition from limited clinical trial use to widespread clinical adoption.

- **Collaborative approach**

  Seamless integration with pharmaceutical developers is critical, from early assay development to final clinical implementation. A good collaborator operates as an extension of the ADC development team, aligning diagnostic strategies with therapeutic goals.

- **Commercialization expertise**

  Successful ADC deployment requires expertise in scaling both companion diagnostics (CDx) and clinical assays. For CDx, this means ensuring timely market readiness and supporting regulatory submissions across multiple jurisdictions. For clinical assays, it involves delivering robust, scalable testing solutions to support routine oncology care, ensuring that ADCs are accessible and effective for patients.

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Quest and PhenoPath

ADC diagnostic expertise

Pharmaceutical companies developing antibody-drug conjugates (ADCs) need more than a diagnostic service—they need a collaborator that can deliver scientific precision, regulatory expertise, and operational excellence throughout the ADC lifecycle.

PhenoPath brings decades of experience in immunohistochemistry (IHC) assay development, with a legacy rooted in some of the earliest advances in monoclonal antibody research. Over the years, PhenoPath has developed more than 200 IHC assays, showcasing its ability to deliver precise, innovative solutions tailored to the needs of complex therapeutic programs. This expertise is complemented by a deep understanding of biomarker-driven therapies, making PhenoPath uniquely equipped to support the rigorous demands of ADC development. Whether validating novel antigen targets or codeveloping companion diagnostics, PhenoPath has the scientific and regulatory expertise to drive successful commercialization.

Quest Diagnostics extends this foundation with unparalleled infrastructure and scale. As one of the largest diagnostic networks in the world, Quest offers nationwide clinical testing capabilities, ensuring that ADCs can be supported from initial development to widespread clinical adoption. This includes the ability to develop and commercialize CDx globally, ensuring that pharmaceutical partners can navigate complex regulatory environments and deliver diagnostics to market efficiently.

In addition to its expertise in CDx, Quest provides robust support for clinical testing, ensuring high-quality, scalable diagnostic solutions for oncology practices across the US. This dual focus on precision and scalability allows Quest and PhenoPath to bridge the gap between groundbreaking science and real-world patient care, enabling ADCs to reach the patients who need them most.

In choosing Quest Diagnostics and PhenoPath, pharmaceutical companies gain access to a comprehensive suite of diagnostic capabilities tailored to the unique challenges of ADC development. From early research to commercialization, Quest and PhenoPath are trusted collaborators in advancing precision oncology.

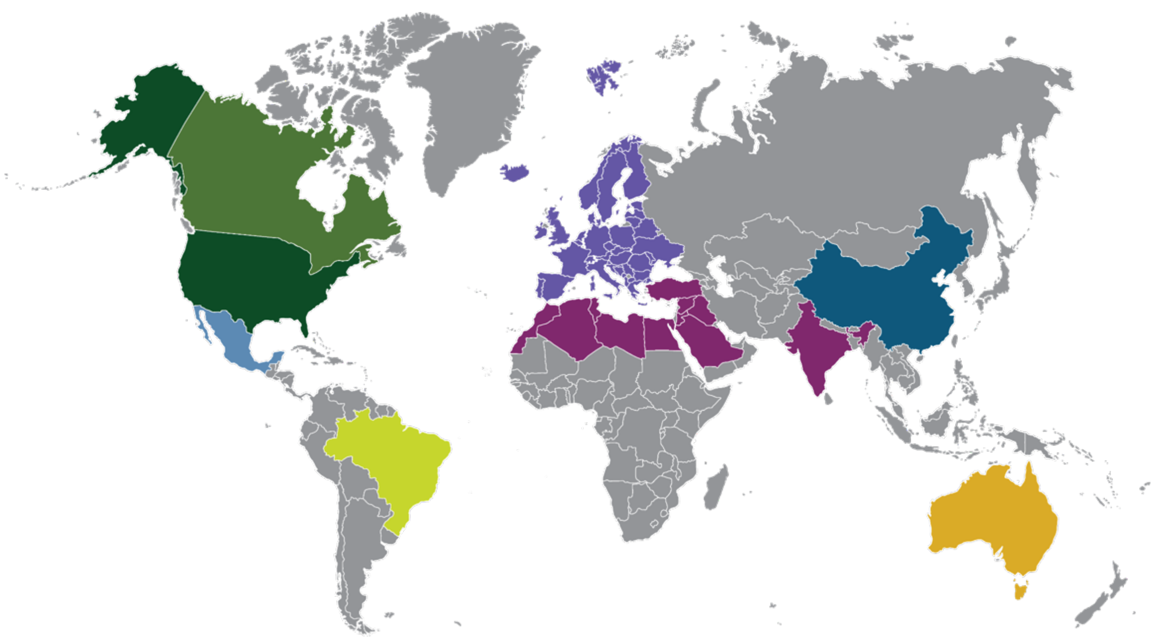
19+
AIRCRAFT SERVICING 53 CITIES

75
COUNTRIES

65%
OF THE WORLD'S POPULATION

25+
TOTAL PROGRAMS

10K
COLLECTION POINTS



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Conclusion

Antibody-drug conjugates represent a powerful convergence of science and medicine, offering unprecedented precision in cancer treatment.

Their success depends not only on innovative therapeutic design but also on the critical role of diagnostic testing at every stage of development and application. The integration of advanced diagnostics helps ensure ADCs reach the right patients safely and effectively, driving progress in the fight against cancer.

Quest Diagnostics and PhenoPath Laboratories bring the expertise and infrastructure needed to support every phase of ADC development, from preclinical assay design to clinical deployment. With a commitment to precision and innovation, Quest and PhenoPath are trusted allies in advancing the next generation of precision oncology therapies.

To learn more about how Quest Diagnostics and PhenoPath can support your ADC development project, contact us today to discuss your unique needs and challenges.

Quest Diagnostics thought leader

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Chief Clinical Officer, Molecular Diagnostics
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Contact us to discover how our precision diagnostics can help power the future of your antibody-drug conjugates and other innovations.

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