

• WHITE PAPER

Rare Diseases vs. Rare Tumor Types

A comparative analysis of epidemiology,
diagnostic pathways, regulatory frameworks,
and clinical management strategies

A Rare Expertise White Paper

For rare disease marketing and medical affairs professionals

rareexpertise.com

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Executive Summary

Rare diseases and rare tumor types represent two overlapping yet fundamentally distinct categories within medicine. While both share low prevalence and face common systemic barriers — including diagnostic delays, limited therapeutic options, and fragmented care pathways — significant differences exist in how each is defined, diagnosed, managed, and regulated.

This white paper provides a structured comparison across six critical dimensions: epidemiology and definitions, diagnostic challenges, molecular and genetic basis, regulatory frameworks, clinical management paradigms, and emerging therapeutic strategies. The analysis draws on published literature, regulatory guidance documents, and real-world clinical experience to identify where pathways converge and where they fundamentally diverge.

7,000+

rare diseases identified to
date

AFFECTING 1 IN 17 PEOPLE
OVER A LIFETIME

5–7 yrs

average diagnostic delay
for rare disease patients

BEFORE CONFIRMED
DIAGNOSIS

20–24%

of all cancers fall into the
rare tumor category

IN AGGREGATE

Key Findings

- Rare diseases are predominantly defined by prevalence thresholds, while rare tumor types are classified by histological, molecular, and anatomical criteria that may shift as reclassification occurs.
- Diagnostic odysseys are a hallmark of both categories, but the trajectory differs: rare disease patients often navigate years without a label, while rare tumor patients typically receive an oncologic diagnosis quickly but face uncertainty around subtype classification and optimal treatment selection.

- The molecular revolution has disproportionately benefited rare tumors through precision oncology, yet rare non-oncologic diseases increasingly leverage the same genomic tools.
- Regulatory orphan drug frameworks technically apply to both but were originally designed with rare diseases in mind; rare tumor types often benefit from accelerated pathways that intersect with broader oncology regulations.
- Multidisciplinary tumor boards and reference center networks are more formalized for rare cancers; equivalent expert network structures for rare diseases remain variable globally.

SECTION 01

Definitions and Epidemiological Landscape

1.1 Defining Rare Diseases

The definition of a rare disease is primarily a regulatory and epidemiological construct based on prevalence. In the United States, the Orphan Drug Act of 1983 defines a rare disease as one affecting fewer than 200,000 Americans. The European Union applies a threshold of fewer than 5 in 10,000 individuals. These prevalence-based definitions encompass an extraordinarily heterogeneous group of conditions — ranging from monogenic metabolic disorders such as Gaucher disease to rare autoimmune conditions, rare infectious diseases, and syndromic presentations with multisystem involvement.

Critically, there are over 7,000 rare diseases identified to date, and collectively they affect an estimated 300 million people worldwide. Despite this aggregate burden, any individual condition may affect only dozens to a few thousand patients globally, creating profound challenges for evidence generation and clinical trial design.

1.2 Defining Rare Tumor Types

Rare tumors are typically defined by a combination of histological rarity, anatomical site, and increasingly, molecular profile. In the European context, RARECARE and subsequent initiatives defined rare cancers as those with an annual incidence of fewer than 6 per 100,000. Collectively, rare cancers account for approximately 20–24% of all cancers diagnosed in Europe — paradoxically making the category quite large in aggregate terms, despite individual tumor types each being uncommon.

Rare tumor types include entities such as soft tissue sarcomas, primary brain tumors, rare gynecological malignancies, carcinoid tumors, adrenocortical carcinomas, and a growing list of molecularly defined tumor types — such as NTRK fusion-positive tumors and NUT carcinomas — that transcend anatomical site. The shift toward molecular classification has blurred traditional boundaries, creating tumor-agnostic rare subtypes.

1.3 Epidemiological Comparison

DIMENSION	RARE DISEASES	RARE TUMOR TYPES
Prevalence threshold	< 200,000 (US) or < 5/10,000 (EU)	< 6/100,000 annual incidence (EU)
Known entities	~7,000 identified conditions	~200+ distinct rare tumor types
Global burden	~300 million affected worldwide	~4–5 million new cases/year globally
Genetic etiology	~80% have genetic basis	Somatic mutations predominant; germline in ~10–15%
Age at onset	Often pediatric or early adulthood	More common in adults; age-dependent by subtype
Natural history	Often chronic and progressive	Often acute with need for immediate intervention

SECTION 02

Diagnostic Challenges and Pathways

2.1 The Rare Disease Diagnostic Odyssey

One of the most consistently documented features of rare disease is prolonged diagnostic delay. Studies have shown that patients wait an average of 5–7 years from symptom onset to confirmed diagnosis, visiting 8 or more clinicians before receiving an accurate label. This delay stems from multiple factors:

- Low clinician familiarity with individual conditions, particularly in primary care settings.
- Phenotypic heterogeneity and overlap with more common conditions.
- Absence of validated, accessible biomarkers or standardised testing protocols.
- Lack of specialized expertise, particularly in non-academic or rural healthcare settings.
- Fragmented care coordination across multiple specialties.

Genomic sequencing — particularly whole exome and whole genome sequencing — has significantly reduced diagnostic timelines for many rare genetic diseases. Programs deploying rapid genomic sequencing in pediatric intensive care units have demonstrated diagnostic yields of 40–60% within days, transforming outcomes for critically ill patients.

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For the first time in the history of medicine, we have the tools to systematically address the diagnostic odyssey. The challenge is no longer scientific — it is one of access, implementation, and the will to act.

Dr. William Gahl, Director, NIH Undiagnosed Diseases Program, National Institutes of Health

2.2 Diagnostic Challenges in Rare Tumor Types

The diagnostic journey for rare tumor patients differs in important ways. Patients typically receive an oncologic diagnosis relatively quickly, as symptoms such as mass formation, bleeding, or organ dysfunction prompt timely imaging and biopsy. However, accurate subtype classification — which directly drives treatment decisions — remains challenging:

- Pathological classification of rare tumors requires specialized expertise. Misclassification rates in sarcoma, for example, can reach 20–25% when reviewed outside dedicated reference centers.
- Molecular diagnostics — NGS panels, FISH, IHC — are increasingly required for precise classification but are not uniformly available or reimbursed.

- For molecularly defined tumor types such as NTRK-positive cancers, testing must occur to unlock targeted therapy eligibility, yet pan-cancer testing algorithms are not yet universally implemented.
- Rare tumor diagnoses often require expert second opinion from specialized sarcoma, neuroendocrine, or other rare cancer centers, introducing delays in treatment initiation.

20–25%

Sarcoma misclassification rate

WHEN REVIEWED OUTSIDE REFERENCE CENTERS

40–60%

Diagnostic yield of rapid NICU sequencing

WITHIN DAYS, FOR CRITICALLY ILL PATIENTS



Pathological misclassification is not an academic footnote in rare cancers — it is a treatment error. ***A sarcoma diagnosed incorrectly is a sarcoma treated incorrectly,*** and the consequences for the patient can be irreversible.

Dr. George Demetri, Director, Ludwig Center at Harvard; Dana-Farber Cancer Institute

Molecular and Genetic Underpinnings

3.1 Rare Diseases: Predominantly Germline and Mendelian

Approximately 80% of rare diseases have an identified genetic basis, most commonly involving germline mutations in single genes. These may follow autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance patterns. The genetic architecture is typically straightforward in that the causative mutation is present in every cell of the body and is heritable.

Next-generation sequencing technologies, gene panels, and whole exome/genome sequencing have transformed rare disease genetics. International consortia such as the Undiagnosed Diseases Network and Solve-RD have leveraged data sharing and functional genomics to identify causative variants in previously undiagnosed patients.

3.2 Rare Tumors: Predominantly Somatic, with Germline Overlap

Rare tumor types are primarily driven by somatic mutations — acquired genetic changes occurring in tumor cells that are not present in germline tissue. These include driver mutations, chromosomal translocations (particularly common in sarcomas and hematologic malignancies), copy number alterations, and epigenetic changes.

However, a meaningful subset of rare tumors are associated with hereditary cancer syndromes: Li-Fraumeni syndrome (TP53) predisposes to sarcomas and other rare malignancies; Lynch syndrome creates risk for rare gynecological and small bowel tumors; SDH-deficient paragangliomas carry germline SDH mutations; and BAP1 tumor predisposition syndrome confers risk for mesothelioma and uveal melanoma. This distinction has profound implications for genetic counselling, cascade testing of family members, and eligibility for germline-targeted therapies.

3.3 Convergence through Precision Medicine

Precision medicine tools developed for oncology — comprehensive genomic profiling, liquid biopsy, transcriptomic analysis — are increasingly being applied to non-oncologic rare diseases. Conversely, the functional genomics and pathway analysis tools developed for rare Mendelian diseases have informed our understanding of cancer biology. This convergence represents an opportunity for cross-disciplinary collaboration and shared infrastructure.

● KEY INSIGHT

Approximately 80% of rare diseases have an identified genetic basis, making genomic testing the most powerful diagnostic tool available.

SECTION 04

Regulatory Frameworks

4.1 Orphan Drug Designation: Shared Architecture, Different Application

Both rare diseases and rare cancers may qualify for orphan drug designation under the prevalence thresholds described above. Designation confers significant benefits: extended market exclusivity, reduced regulatory fees, protocol assistance, and expedited review in some jurisdictions. However, the application differs substantially between the two populations.

For rare non-oncologic diseases, orphan designation has historically been the primary regulatory mechanism for incentivizing drug development, given that market forces alone are often insufficient to drive investment in small patient populations. Gene therapy, enzyme replacement, and substrate reduction therapies for lysosomal storage disorders have relied heavily on these orphan incentives.

For rare cancers, orphan designation coexists with a broader set of oncology-specific expedited pathways, including Breakthrough Therapy Designation, Accelerated Approval based on surrogate endpoints, and tumor-agnostic approvals — providing a richer regulatory toolkit than is typically available to rare disease developers.

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Orphan drug policy was a landmark achievement, but it was designed for an earlier era. As the science has advanced — particularly in oncology — our regulatory frameworks need to evolve with it to ensure patients can access the treatments they need without unnecessary barriers.

Dr. Janet Woodcock, Principal Deputy Commissioner, U.S. Food and Drug Administration

4.2 Tumor-Agnostic Approvals: A Rare Tumor Innovation

A notable regulatory innovation specific to oncology is the tumor-agnostic approval — the approval of a therapy based on a biomarker rather than tumor histology or anatomical site. The FDA approvals of larotrectinib and entrectinib for NTRK fusion-positive cancers, and pembrolizumab for MSI-H/dMMR tumors, exemplify this approach. Rare tumor types disproportionately benefit because a molecularly defined subtype may span multiple histological types, each too small individually to power a conventional trial.

There is no direct analogue to tumor-agnostic approval in the non-oncologic rare disease space, where treatments are almost universally disease-specific. This represents both a gap and an opportunity for regulatory innovation.

DIMENSION	RARE DISEASES	RARE TUMOR TYPES
Primary pathway	Orphan Drug Designation	ODD + Breakthrough, Accelerated Approval, Tumor-Agnostic
Market exclusivity	7 years (US), 10 years (EU)	Same, plus potential basket indication sharing
Surrogate endpoints	Limited and disease-specific	Extensive: ORR, PFS widely accepted
Biomarker-driven approval	Rare, emerging	Established tumor-agnostic framework
Adaptive trial designs	Increasing but still rare	Platform and basket trials are standard practice
Post-market requirements	Variable; REMS common	Confirmatory trials often required

SECTION 05

Clinical Management Paradigms

5.1 Management of Rare Diseases: Chronic, Longitudinal Care

The clinical management of rare diseases is predominantly characterized by chronic, longitudinal care aimed at disease modification, symptom control, and prevention of complications. Management strategies span an enormous range: enzyme replacement for metabolic storage diseases, immunosuppression for rare autoimmune conditions, dietary modification for inborn errors of metabolism, and highly targeted small molecules or gene therapies for specific genetic disorders.

- **Life-long treatment:** most rare diseases require ongoing therapy with no prospect of cure, necessitating durable adherence and safety monitoring frameworks.
- **Multiorgan involvement:** many rare diseases affect multiple organ systems, requiring coordinated input from numerous specialists.

- **Transition of care:** a growing population of pediatric rare disease patients requires effective transition to adult care models that may be poorly equipped for their needs.
- **Patient-reported outcomes:** given the heterogeneity of manifestations, patient-reported outcomes and quality-of-life measures are increasingly central to clinical management.
- **Caregiver burden:** rare diseases frequently impose substantial burden on family caregivers, particularly when pediatric patients are involved or when cognitive and functional impairment is present.

5.2 Management of Rare Tumor Types: Acute, Curative Intent

Rare tumor management operates within a fundamentally different time horizon. Most treatment is pursued with curative or disease-control intent and is organized around defined treatment episodes: surgery, radiotherapy, chemotherapy cycles, and increasingly, targeted or immunotherapy regimens.

- **Multidisciplinary tumor boards:** formal expert review of imaging, pathology, and treatment plans is the standard of care for rare cancers, mandated by guidelines and accreditation bodies in many jurisdictions.
- **Reference center concentration:** guidelines consistently recommend management at or in consultation with specialized reference centers — a model formalized in Europe through the European Reference Networks for rare cancers (EURACAN).
- **Surgery as cornerstone:** for many solid rare tumors, surgical resection — often highly specialized — remains the primary curative modality. Surgical volume-outcome relationships are particularly pronounced.
- **Systemic therapy complexity:** treatment increasingly requires access to molecularly targeted therapies, clinical trials, and off-label use, requiring expert knowledge of an evolving evidence base.

5.3 Shared Management Challenges

Despite these differences, both rare disease and rare tumor patients share important management challenges: limited evidence base makes randomized controlled trials difficult or impossible, so both fields rely heavily on registries, natural history studies, single-arm trials, and real-world evidence; off-label drug use is common in both settings, creating reimbursement, liability, and

informed consent complexities; access to specialized expertise is geographically uneven, disadvantaging patients in rural or low-resource settings; and diagnostic uncertainty, disease rarity, and limited peer community are sources of significant psychological distress for both patient populations.

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We have built two parallel worlds — rare disease on one side, rare cancer on the other — when the patients we serve often live in both. ***The silos we maintain in research, regulation, and care delivery are institutional.*** They are not biological.

Yann Le Cam, Chief Executive Officer, EURORDIS — Rare Diseases Europe

Clinical Trials and Emerging Therapies

6.1 Trial Design in Small Populations

Conventional randomized controlled trial design is inherently challenging when patient populations are small. Both rare disease and rare tumor research have been at the forefront of methodological innovation, though specific solutions differ by therapeutic area.

For rare diseases, key approaches include N-of-1 trials for highly individualized therapies, natural history studies as external controls, Bayesian adaptive designs, and master protocols leveraging shared infrastructure across multiple rare conditions. Patient registries as platforms for observational and interventional research are particularly well-developed in rare disease.

For rare tumors, basket trials — enrolling patients based on shared biomarkers across multiple tumor types — have emerged as a powerful design. Platform trials such as NCI-MATCH and ESMART allow molecularly selected patients to receive matched therapies across histologies, enabling efficient evaluation of targeted agents in otherwise insufficiently small populations.

6.2 Gene and Cell Therapies: Primarily Rare Disease

Transformative gene therapies — including gene replacement, gene editing approaches, and ex vivo cell therapy — have emerged primarily in the rare genetic disease space, where a single causative genetic defect represents a clear therapeutic target. Regulatory approvals for gene therapies in hemophilia, retinal dystrophy, spinal muscular atrophy, and beta-thalassemia represent a paradigm shift in rare disease management.

While gene therapy applications in oncology exist — CAR-T cell therapy being the most prominent — these are distinct from germline or somatic gene correction approaches that characterize rare disease gene therapy. The manufacturing, delivery, and pricing challenges of gene therapies are particularly acute in rare diseases given small patient volumes.

6.3 Targeted and Immunotherapy: Primarily Rare Tumors

Precision oncology — the use of molecularly targeted small molecules and immune checkpoint inhibitors — has transformed the management of several rare tumor types. NTRK inhibitors, RET inhibitors, ALK inhibitors, BRAF-targeted combinations, and IDH inhibitors represent molecularly

guided therapies that benefit specific rare tumor populations defined by molecular alteration rather than histological subtype.

Immunotherapy has proven effective in microsatellite instability-high tumors — a molecular phenotype found across a variety of rare tumor types — as well as in Merkel cell carcinoma, rare melanoma subtypes, and other rare cancers. The field is evolving toward combination strategies and biomarker-guided patient selection.

● EMERGING CONVERGENCE

Small molecules targeting specific mutant proteins, antisense oligonucleotides, and RNA interference therapies are increasingly resembling the precision oncology toolkit in their target specificity. The regulatory and scientific boundaries between these areas are becoming more permeable.

25–50%

Diagnostic yield of exome/genome
sequencing
IN PREVIOUSLY UNDIAGNOSED RARE DISEASE
PATIENTS

~80%

Of rare diseases have a known genetic basis
MAKING GENOMIC TESTING THE MOST POWERFUL
TOOL

SECTION 07

Policy Recommendations

Based on the comparative analysis above, the following recommendations are offered for stakeholders across the rare disease and rare oncology ecosystems:

- 1 Harmonize Registry Infrastructure.** National and international patient registries for both rare diseases and rare tumors are critical evidence-generation tools but remain siloed. Regulatory agencies, research networks, and patient organizations should invest in interoperable registry infrastructure that allows data sharing and cross-condition analysis.
- 2 Expand Tumor-Agnostic Frameworks to Rare Diseases.** The success of biomarker-driven tumor-agnostic approvals in oncology suggests an opportunity to develop analogous frameworks for rare diseases where a therapeutic mechanism applies across multiple conditions sharing a common molecular defect.
- 3 Mandate Second Opinion Access for Rare Tumors.** Given documented misclassification rates and treatment implications, regulatory and health system frameworks should mandate or strongly incentivise access to second opinion review at designated reference centers prior to treatment initiation.
- 4 Accelerate Genomic Diagnostics Reimbursement.** Both rare disease patients and rare tumor patients benefit from comprehensive genomic profiling, yet reimbursement remains inconsistent. A unified policy framework would reduce access inequity.
- 5 Develop Cross-Disease Training Programs.** The scientific and clinical communities managing rare diseases and rare tumors remain largely separate. Investment in cross-disciplinary training, joint symposia, and shared research fellowships would accelerate knowledge transfer.
- 6 Center Patient Advocacy in Research Governance.** Health systems, research funders, and pharmaceutical developers should embed patient advocacy representatives in governance structures from early research planning through post-market surveillance.

SECTION 08

Conclusion

Rare diseases and rare tumor types share a common challenge: small patient populations, limited evidence, and significant unmet clinical need. Yet a detailed comparative analysis reveals that the pathways to diagnosis, the molecular and biological underpinnings, the regulatory frameworks, and the clinical management paradigms differ in important and consequential ways.

Rare disease patients endure protracted diagnostic odysseys in search of a label, and management is predominantly chronic, requiring durable, multidisciplinary care models. Rare tumor patients receive an oncologic diagnosis with relative speed but face critical classification uncertainty that directly impacts treatment; management is acute and increasingly driven by molecular profiling and access to precision therapies.

The regulatory architecture for rare diseases is anchored by orphan drug frameworks, while rare oncology benefits from an additional layer of expedited pathways and tumor-agnostic approval mechanisms. Both spaces are at the forefront of methodological innovation in clinical trial design, with basket trials and natural history platforms increasingly shaping evidence generation.

As genomic medicine matures, the artificial boundaries between these two domains will increasingly give way to a shared precision medicine infrastructure. Stakeholders who recognize both the commonalities and the distinctions between rare diseases and rare tumor types will be better positioned to design policies, develop therapies, and deliver care that meets the complex needs of these underserved patient populations.

Rare Expertise

Rare Expertise is a strategic consultancy focused on helping companies developing and marketing products for patients with rare diseases. Our mission is to shorten the diagnostic and treatment journey in people with rare diseases through better education.

Rare Expertise and the Rare Medical Network work at the intersection of rare disease knowledge, clinical practice, and trusted professional networks. Our focus is on supporting healthcare professionals with credible information and access to expertise — when it matters most.

FOUNDED

Rare Expertise was founded in 2015 by Jack Davis and Jeff Sweeney, who are parents of children with rare diseases, and who both have extensive professional experience in marketing communications and medical education in rare disease markets.