Rare Disease Ecosystem

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Purpose of this document

This document provides an overview of the care system in the context of rare diseases:

- general features of rare diseases,
- diagnostic and treatment journey for patients and clinicians,
- personal, economic and financial impact
- the nature of orphan drugs for the treatment of rare diseases.

Rare diseases

- have a known known and definable impact on the healthcare system,
- have common features.

There is little research for most rare diseases

- personal and economic burden,
- costs across the care pathway,
- evidence on the diagnostic treatment process such as delays and misdiagnosis.

Rare diseases can be understood in aggregate. That means general findings can be used as proxy measures for specific rare diseases, and act as a probe into that patient population's likely experience and provide insight into measures of burden.

'Precision' and 'personalised' medicine in effect makes every person a cohort of one, with corresponding personalised treatment.

That also means that the treatment populations of medicines:

- have defining features (inclusion/exclusion criteria) couple of clinical guidelines and protocols
- are identified through biomarkers, or similar

Top rare diseases which have diagnostic difficulties

- Mucopolysaccaridosis
- Severe combined immune deficiency
- Pompe's disease
- Myelodysplastic syndrome
- Fabry's disease
- Primary pulmonary arterial hypertension
- Urea cycle defects
- Cystic fibrosis
- Ornithine transcarbamylase (OTC) deficiency
- Fanconi anemia
- McArdle's disease /Glycogenosis
- Glaucoma in children
- Wilson's disease
- Ataxia telanglectasia
- Scleroderma
- Acromegaly
- Amyotrophic lateral sclerosis
- Ehlers-Danlos syndrome

Blöß S, Klemann C, Rother A-K, Mehmecke S, Schumacher U, Mücke U, et al. Diagnostic needs for rare diseases and shared prediagnostic phenomena: Results of a German-wide expert Delphi survey. Palau F, editor. PLOS ONE;12(2):e0172532.

Why and how rare disease diagnoses are difficult and why patients get misdiagnosed

Patient centred	Clinician centred	Healthcare System centred
1. failure to convince doctor something is wrong 2. parents struggling to convince doctor something is wrong with child 3. not being believed 4. imprecise description of symptoms (vague, generalised) 5. frustration 6. self-doubt 7. "feeling different"	1. poor history taking 2. not putting symptoms together (pattern recognition, familiarity) 3. poor clinical reasoning (failure within differential diagnosis) 4. patient looks well hence no action 5. label patient as time-consuming, "dissembler" 6. gender-inappropriate reasoning 7. correlate symptoms to menopause 8. age-related stereotyping 9. patient labelled as somatising 10. lack of classical symptoms 11. Zebra Retreat (fear of making an unusual diagnosis)	1. patient treated but doesn't get better 2. many clinical encounters with same or different clinicians/doctors/facilities 3. no defined clinical pathway, no guidelines, no referral guidelines 4. wrong psychological/somatic diagnosis 5. long journey (time) to correct diagnosis 6. time-consuming structural workflow/process to arrive at correct diagnosis (many steps, many people, many facilities) 7. perverse/inappropriate financial incentives, payments, reimbursements

Blöß S, Klemann C, Rother A-K, Mehmecke S, Schumacher U, Mücke U, et al. Diagnostic needs for rare diseases and shared prediagnostic phenomena: Results of a German-wide expert Delphi survey. Palau F, editor. PLOS ONE;12(2):e0172532.

Known sources of delay along the patient journey

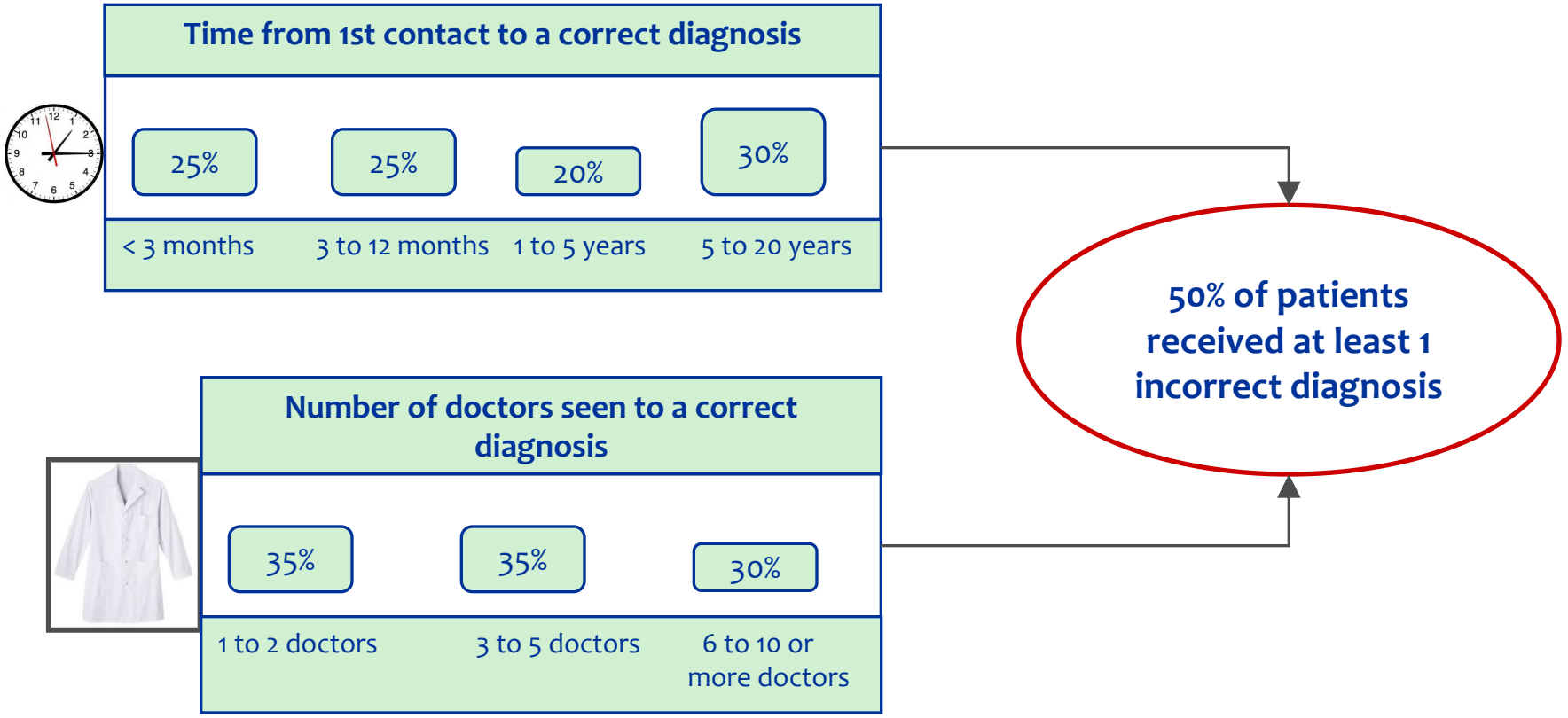
Patient centred	Clinician centred	Healthcare System centred (varies by country)
1. low adherence / compliance with treatment 2. low literacy (general, treatment specific) 3. no patient network or weak patient support groups 4. patient denial, avoidance 5. lack of information on access to referral or treatment options	1. lack of clinical insight by clinicians arising from weak access to high quality information	1. lack of treatment facilities (specialist, secondary, tertiary referral/dx/tx) 2. rate limiting supply of health professionals 3. weak referral system, or lack of access to relevant clinical expertise 4. access difficulties (travel, locations) 5. health provider financial barriers (treatment for payment and/or reimbursement eligibility 6. patient financial barriers (insurance eligibility, co-insurance, co-payments, social care, out-of-pocket costs)

Blöß S, Klemann C, Rother A-K, Mehmecke S, Schumacher U, Mücke U, et al. Diagnostic needs for rare diseases and shared prediagnostic phenomena: Results of a German-wide expert Delphi survey. Palau F, editor. PLOS ONE;12(2):e0172532.

The patient experience

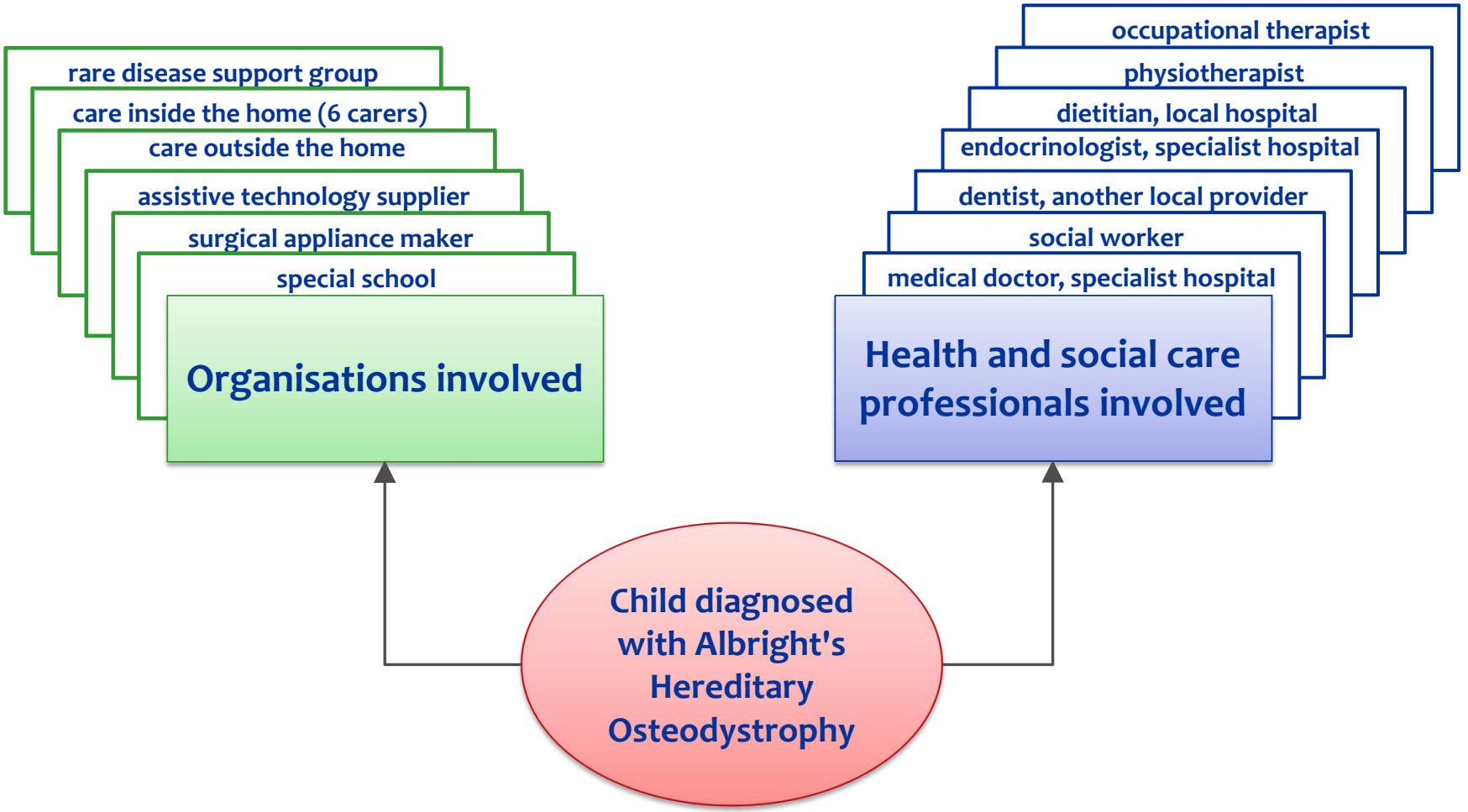
APSU Rare Diseases Impacts on Families Study group, Zurynski Y, Deverell M, Dalkeith T, Johnson S, Christodoulou J, et al. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. Orphanet Journal of Rare Diseases. 2017 Dec;12(1).

The diagnostic journey can be long, involve many clinical encounters with high risk of misdiagnosis



Molster C, Urwin D, Di Pietro L, Fookes M, Petrie D, van der Laan S, et al. Survey of healthcare experiences of Australian adults living with rare diseases. Orphanet Journal of Rare Diseases. 2016 Dec ;11(1).

Typical family challenges with rare diseases: example of Albright's Hereditary Osteodystrophy



Holm BB, Jensen L, Only the Strong Survive, Rare Diseases Denmark, 2014

People with rare diseases experience significant real world challenges

People living with rare diseases ...

65%

have to visit different health, social, and local support services

patients report 10 to 30 patient health and social care professionals as contacts [2]

67%

say health and social care services communicate badly with them

38%

and their carers were absent from work for health-related issues for over 30 days in the past year

64%

have a female (e.g. mother) as the primary care giver

[1] Eurordis, Juggling care and daily life: the balancing act of the rare disease community, Eurobarometer, May 2017.
[2] Rare Disease Denmark, Only Strong Survive, 2010.

People with rare diseases perceive professionals to be ill-prepared

People living with rare diseases ...

75%

consider teachers, social works and other care givers have a deficient knowledge of rare diseases and their consequences

71%

say health and social care services professionals are not sufficiently prepared to give care and are not sensitised to the issues of rare diseases

67%

say care providers communicate badly or very badly with each other in provision of care services

Eurordis, Juggling care and daily life: the balancing act of the rare disease community, Eurobarometer, May 2017.

People living with rare diseases do not feel well informed

People living with rare diseases ...

70%

do not feel well-informed of their social care rights and entitlements

73%

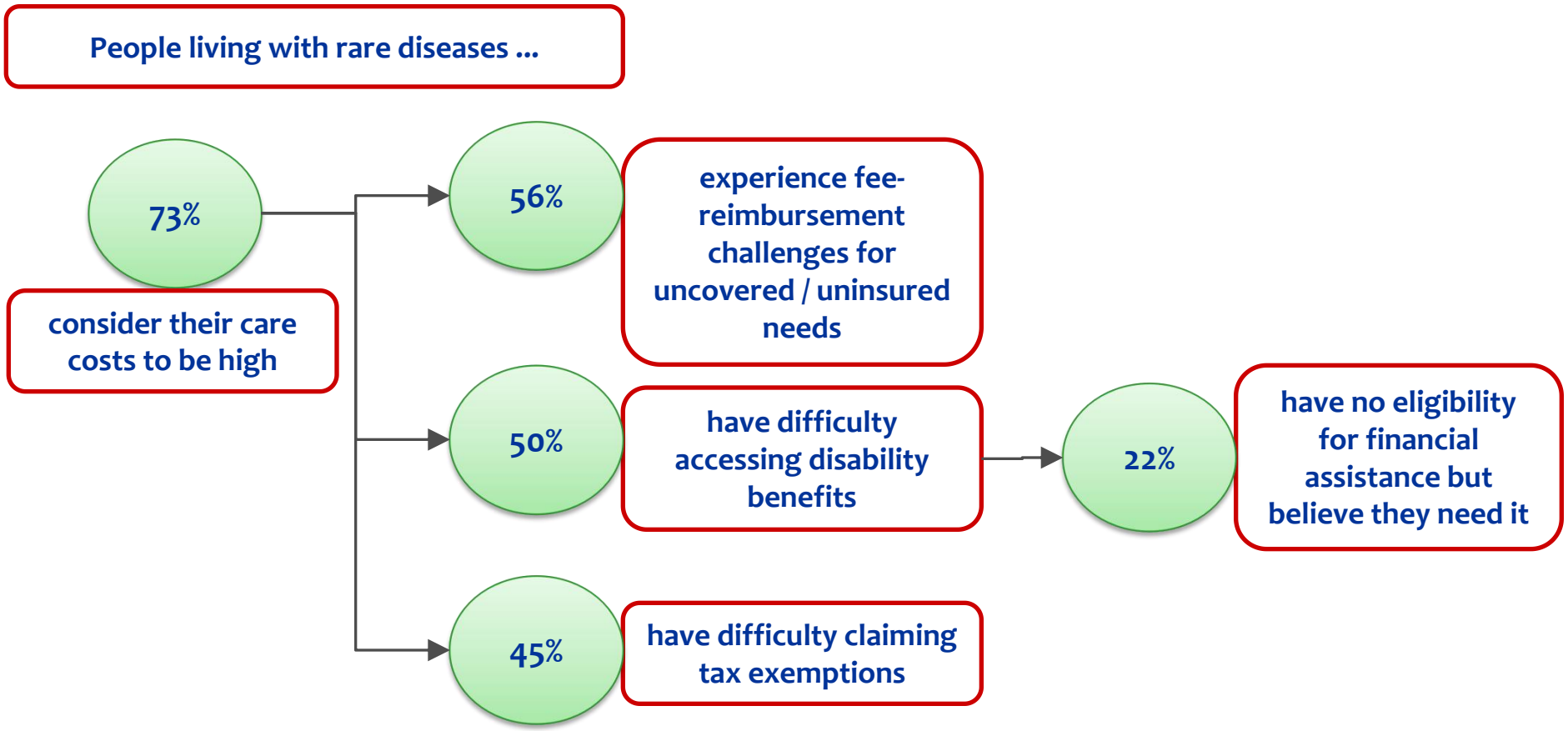
do not feel well-informed about financial assistance

47%

do not feel well-informed about medical care services

Eurordis, Juggling care and daily life: the balancing act of the rare disease community, Eurobarometer, May 2017.

People living with rare diseases struggle with financial challenges



Eurordis, Juggling care and daily life: the balancing act of the rare disease community, Eurobarometer, May 2017.

Diagnosis, access to healthcare shows ethnic / racial variation [1] and discrimination [5]

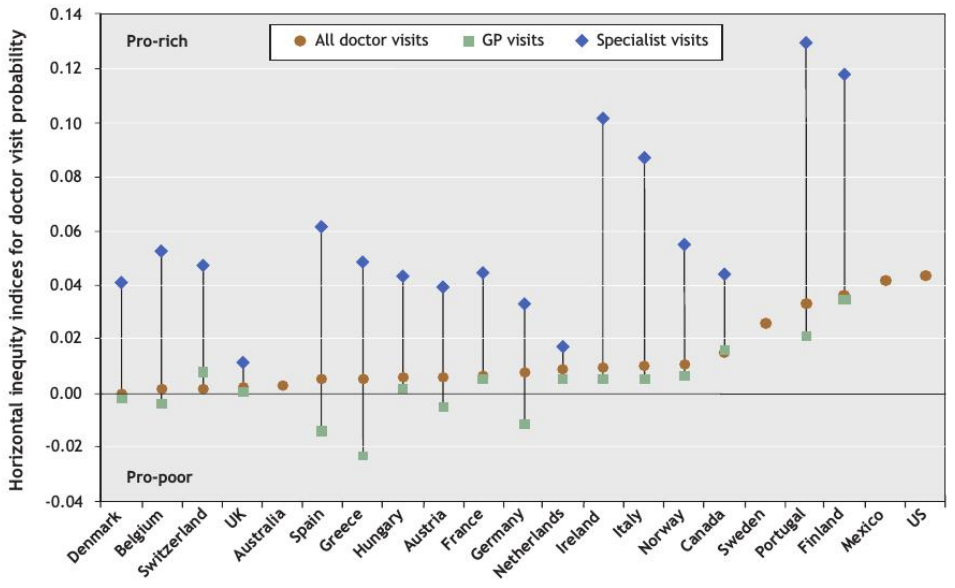


Fig. 4: Horizontal inequity (HI) indices for the annual probability of visiting a doctor in 21 OECD countries. Countries are ranked by HI for doctor visits. German general practitioner (GP) and specialist indices reflect data obtained in the 1996 ECHP.

"... after controlling for need differences, the rich are significantly more likely to see a specialist than the poor and, in most countries, more frequently." [2]

Signals

- Research shows there are social, ethnic and racial determinants of unequal access to healthcare services [2]
  - Specific research shows that leptin and insulin resistance varies by ethnicity and race [3]
  - There is racial disparities in diabetes mellitus hospitalisation [4]

[1] Bhopal RS. Racism in health and health care in Europe: reality or mirage? The European Journal of Public Health. 2007;17(3):238–241.

[2] van Doorslaer E. Inequalities in access to medical care by income in developed countries. Canadian Medical Association Journal. 2006 Jan 17;174(2):177–83.

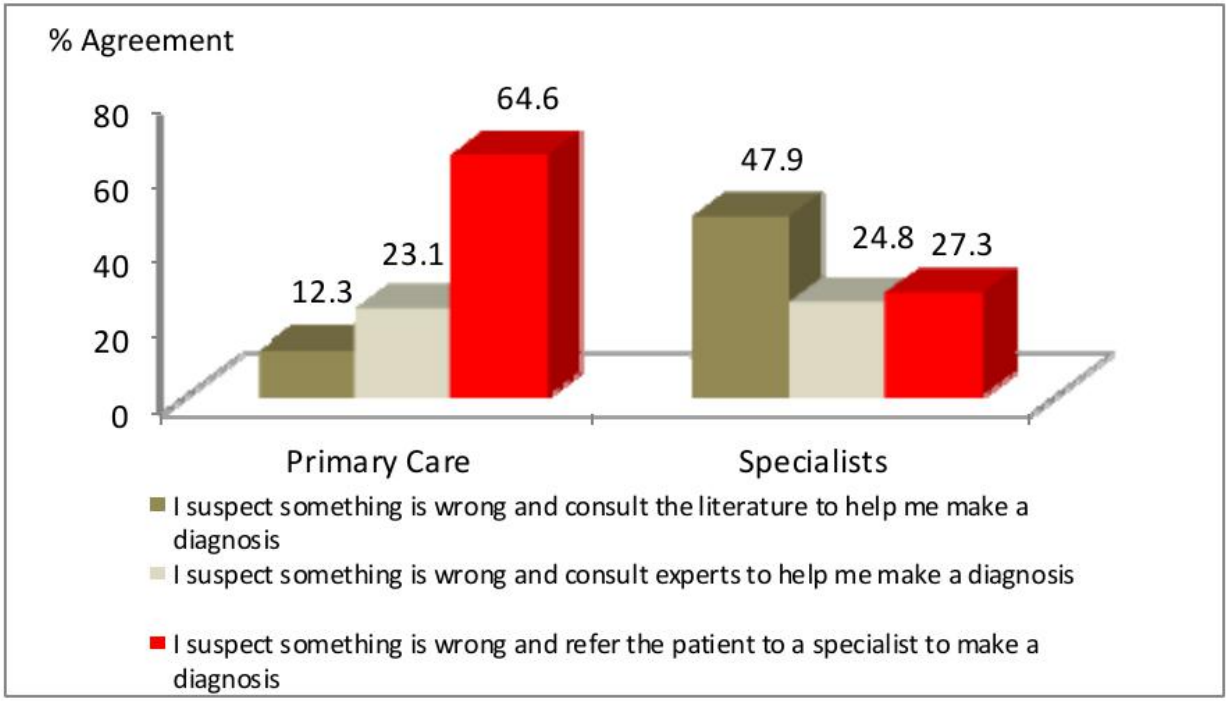
[3] Mente A, others. Ethnic Variation in Adiponectin and Leptin Levels and Their Association With Adiposity and Insulin Resistance and Their Association with Adiposity and Insulin Resistance. Diabetes Care. 2010;33:1629–34.

[4] Ruhl C, Everhart J. Leptin concentrations in the United States relations with demographic and anthropometric measures. Am J Clin Nutr. 2001;74:295–301.

[5] Wan TTH, Lin Y-L, Ortiz J. Racial Disparities in Diabetes Hospitalization of Rural Medicare Beneficiaries in 8 Southeastern States. Health Services Research and Managerial Epidemiology. 2016 Apr 27 ;3:233339281667163.

The doctor's experience

How doctors deal with learning about rare diseases for diagnosis

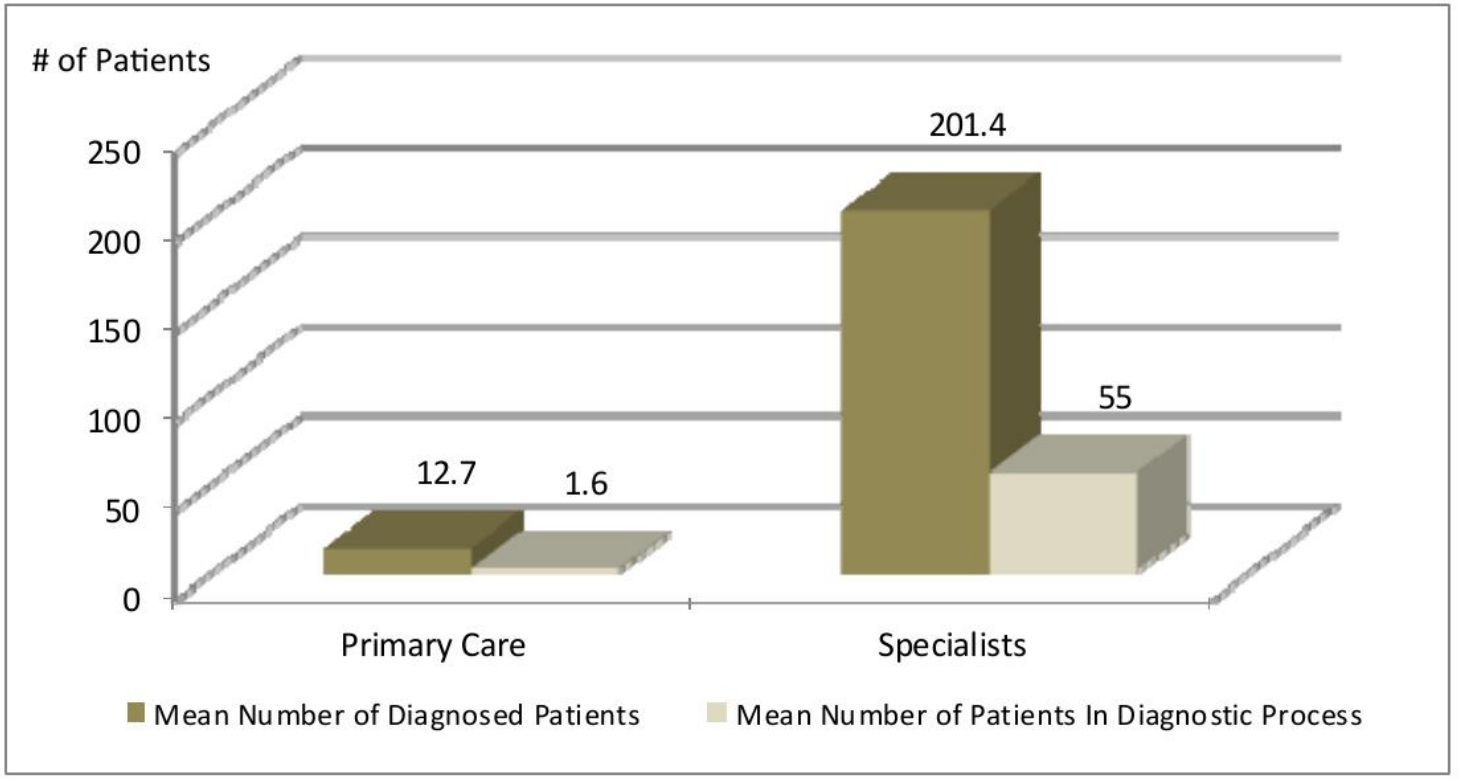


Signal

- specialists depend on access to quality literature as diagnostic support
- primary care doctors depend on availability and access to specialists for diagnosis
- specialists also depend on a network of other specialists to assist in diagnosis

Engel P. et al. Physican and patient perceptions regarding physician training in rare diseases: the need for stronger educational initiatives for physicians. The Journal of Rare Disorders. 2013;1(2):1–15.

Rare disease specialists will have more rare disease patients than primary care doctors

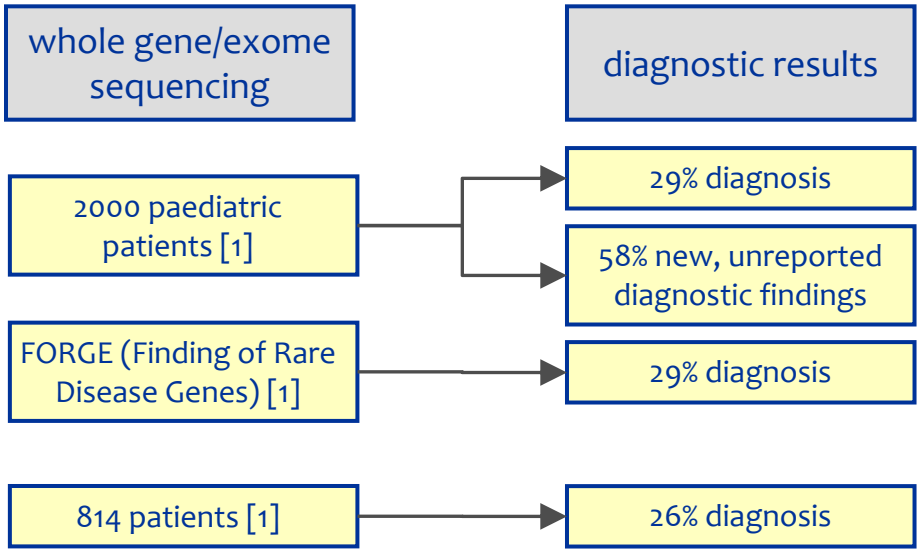


Signal

•The management of people with rare diseases is better understood as a specialist activity.

Engel P. et al. Physican and patient perceptions regarding physician training in rare diseases: the need for stronger educational initiatives for physicians. The Journal of Rare Disorders. 2013;1(2):1–15.

Genetic sequencing is effective in rare conditions and a key enabler of precision medicine [2]



Signal

•The technical costs of whole genome sequencing (whole genome/whole exome) are falling, and there is evidence it is efficacious, suggesting a positive value for money assessment.

[1] Christensen K, Dukhovny D, Siebert U, Green R. Assessing the Costs and Cost-Effectiveness of Genomic Sequencing. Journal of Personalized Medicine. 2015 Dec 10;5(4):470–86.

[2] Schuster J, Khan TN, Tariq M, Shaiq PA, Mäbert K, Baig SM, et al. Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy. BMC medical genetics. 2014;15(1):71.

Doctors feel ill-prepared to use genetic data and need assistance developing proficiencies

Theme	Description	Example
Primary		
Genetic literacy	Comments about understandings of genetics, genomics or WGS	"A lot of recessive stuff can have a phenotype, which I didn't know about." [P17]
Concerns about preparedness	Concerns about being unprepared to interpret, explain, or respond to WGS results	"I'm a little bit apprehensive about how much information may be provided and being able to convey the information in a clear manner." [P19]
Motivations about developing proficiencies	Statements about enrolling in the study to prepare for WGS use in the future	"[I] have followed the world of genomics and thought this would be a chance to learn more." [C21]
Secondary		
Previous experiences	Professional and personal experiences with genetic services	"I got emails from patients saying, 'Can you call my closest Quest Laboratory and order the BRCA gene for me?'" [P16]
Education sessions	Comments about the study-provided educational curriculum	"I actually learned a lot from those sessions, you know. Not only in terms of the reports themselves but how to look at mutations." [P15]
Response to reports	Comments about the WGS or family history reports	"[The reports have] about the right level of complexity." [C08]
Genome Resource Center	Comments about using the Genome Resource Center for assistance	"I'm going to use them as a way to educate me, initially, about what these conditions are." [C09]
Infrastructure	Comments about policies, programs, and tools that facilitate or hinder the use of WGS	"They won't then be able to store [WGS] reports in the medical record, because there is no format for doing that yet." [C08]
Genetic counselors' role	Anticipated use of genetic counselors to respond to WGS reports	"I would anticipate my leaning heavily on the genetic counselor." [C18]
Information seeking	Resources physicians expected to use to help interpret WGS reports	"... refer to the genetic counselor for a more detailed explanation for a specific condition." [P11]

Signal

- Doctors have a range of specific needs in order to work with genetic data in diagnosis and treatment selection.

Christensen KD, Vassy JL, Jamal L, Lehmann LS, Slashinski MJ, Perry DL, et al. Are physicians prepared for whole genome sequencing? a qualitative analysis: Are physicians prepared for whole genome sequencing? Clinical Genetics. 2016 Feb;89(2):228–34.

Need for specific information varies by the context of the doctor's work

	Primary Care Physician	Specialist
Genetic Expertise	Limited knowledge of genetics	Familiar with genetics
Use of Genetic Information	Experienced in use of novel information as a first-line provider of care	Apprehension about decision making and acting appropriately with new genetic findings

Signal

•Doctors in primary care say they lack sufficient knowledge of genetics while specialists are concerned about their ability to interpret and apply specific results in patient care.

Christensen KD, Vassy JL, Jamal L, Lehmann LS, Slashinski MJ, Perry DL, et al. Are physicians prepared for whole genome sequencing? a qualitative analysis: Are physicians prepared for whole genome sequencing? Clinical Genetics. 2016 Feb;89(2):228–34.

The economics of orphan drugs

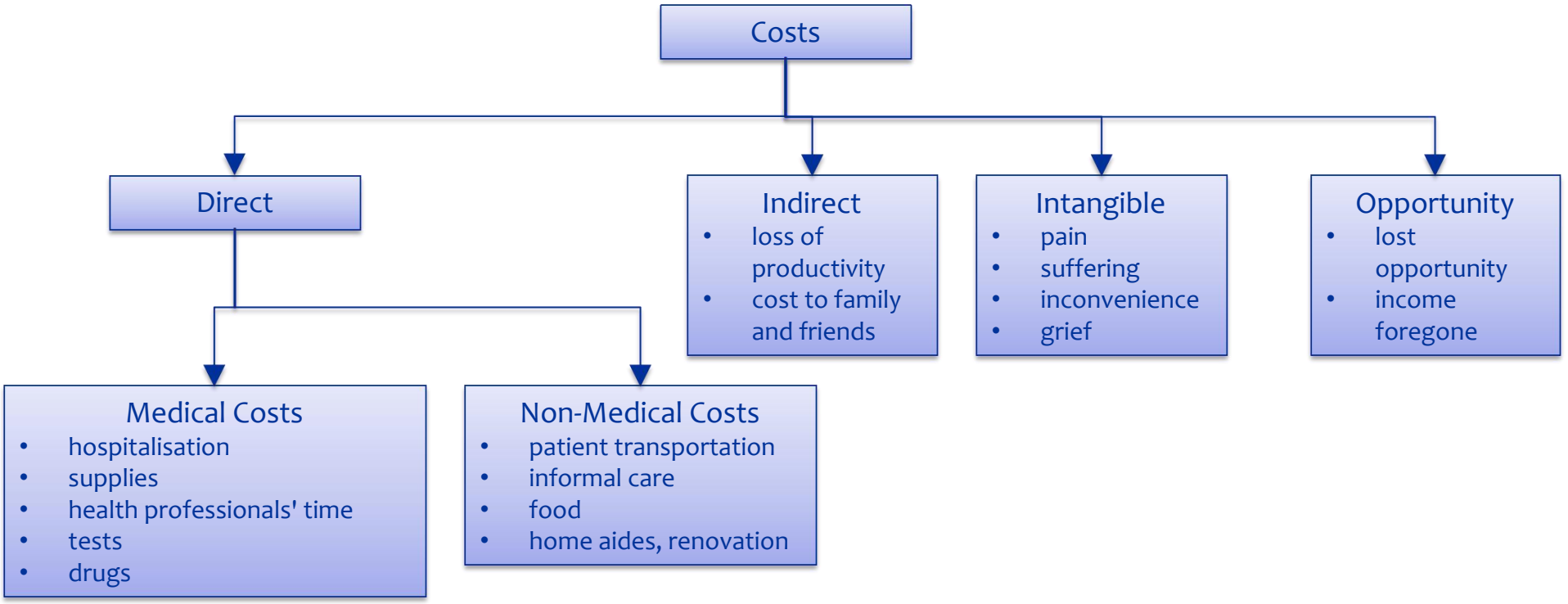
Graf von der Schulenburg J-M, Frank M. Rare is frequent and frequent is costly: rare diseases as a challenge for health care systems. The European Journal of Health Economics. 2015 Mar;16(2):113–8.

Orphan drugs are increasing in share of medicines, with a rising impact on budgets.

"For many years, the market for orphan drugs has reflected a sort of unwritten agreement that small patient numbers could allow public and private insurers to maintain reasonable access to orphan drugs despite much higher prices. Innovation was given suitable rewards, patients received rapid insurance coverage, and insurers were able to absorb high per-patient costs without seeing destabilizing impacts to their overall budgets. However, the orphan drug landscape is shifting rapidly, with great promise for patients, but also with a growing sense of peril for health care budgets."

Ollendorf DA, Chapman R, Pearson SD. Assessing the Effectiveness and Value of Drugs for Rare Conditions. Institute for Clinical and Economic Review. 2017

Rare diseases have a specific cost taxonomy



Molster C, Urwin D, Di Pietro L, Fookes M, Petrie D, van der Laan S, et al. Survey of healthcare experiences of Australian adults living with rare diseases. Orphanet Journal of Rare Diseases. 2016 Dec ;11(1).

Costs can be localised into four areas which arise from the structure of the care pathway

Patients report costs arising from

1. poor care coordination and failure of care processes to align particularly between healthcare and social care
2. cost-sharing and eligibility criteria for means testing
3. hidden and unreimbursed costs which impact quality of life

Financial Costs

Costs associated with appointments

- lost income from time off from work
- reduced income earning potential
- childcare
- travel costs (petrol, parking)
- accommodation
- accessible vehicles

Condition management

- private healthcare alternatives
- respite, nursing and home care
- care technologies, telephone, internet
- informal carers time and abilities
- disruption to activities of daily living

Other Costs

Time

- time coordinating care with various agencies
- time spent determining eligibility for (social) care and reimbursement
- time spent waiting for care
- time spent with wrong diagnosis and treatment

Psychosocial, quality of life

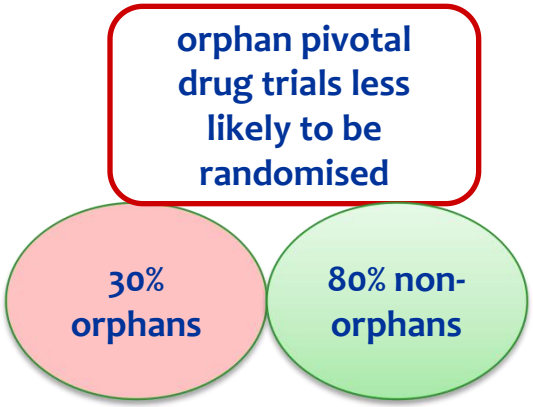
- disruption to schooling, employment and personal time
- relationship impact and social life
- isolation
- identify and self-esteem
- living with uncertainty
- fatigue, anxiety, stress

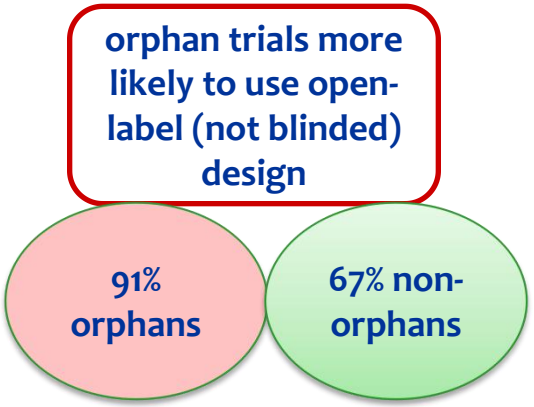
Wider personal context

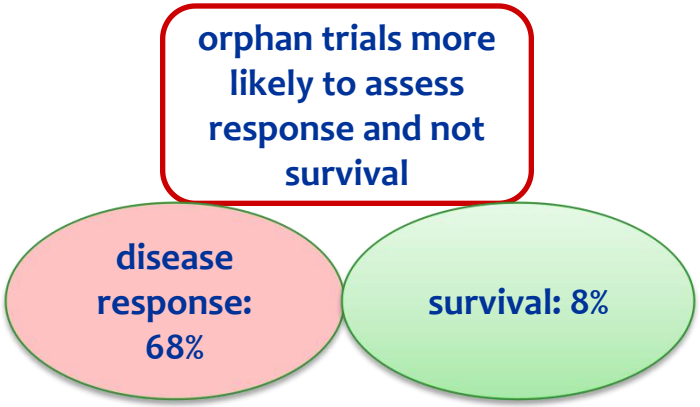
- above costs but applied to informal carers, family and friends, employers and wider social and support networks

Genetic Alliance UK, The hidden costs of rare diseases, 2016.

The evidence base and trial design of orphan drugs differs from non-orphan drug trials







Signal

•Compared to pivotal trials for non-orphan drugs, for recently approved orphan drugs for cancer were more likely to be smaller and to use nonrandomized, unblinded trial designs and surrogate end points to assess efficacy.

Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA. 2011;305(22):2320-2326.

Orphan drugs have high cost per QALY but assessment depends on quality-of-life assumptions [1]

Drug [a]	Indication	Prevalence	QALY	CHEC score [2] [b]
Agalsidase alfa & beta	Fabry	0.22:100,000	€3,282,252	18
Velaglucerase alfa & Imiglucerase	Gaucher	1:100,000	€432,540	19
Alglucosidase alfa	Pompe	1:14,000	€326,791	16
Eculizumab	Paroxysmal Nocturnal Haemoglobinuria	1: 500 000	€1,620,256	17
[a] assessed against current standard of care [b] CHEC: 19 point Consensus on Health Economic Criteria, higher is better				

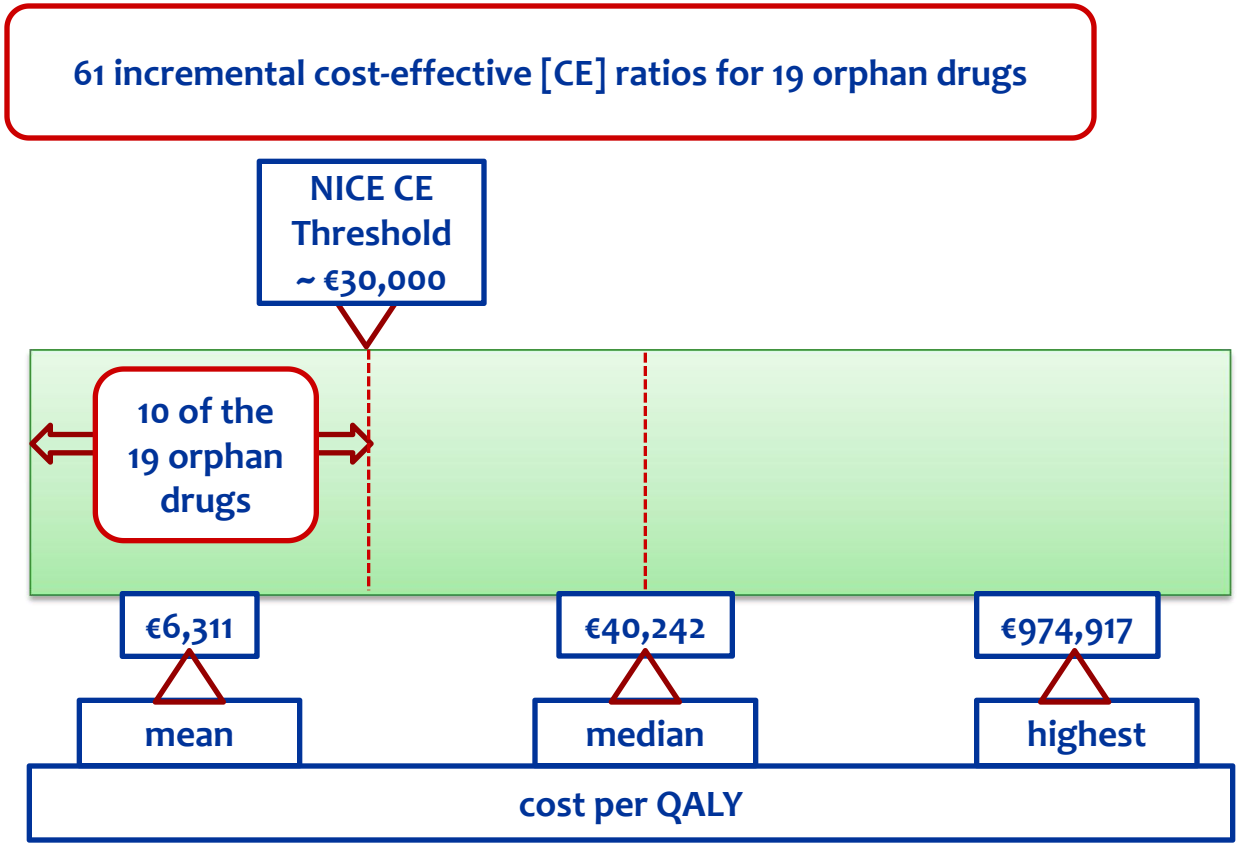
Signal

•Orphan drugs have high cost per QALY, BUT this study shows that the underlying study assumptions about quality of life, whether perfect, or just survival which leads to unrealistic ICURs (utility ratios)

[1] Schuller Y, Hollak CEM, Biegstraaten M. The quality of economic evaluations of ultra-orphan drugs in Europe – a systematic review. Orphanet Journal of Rare Diseases. 2015 Dec;10(1).

[2] Evers S, Goossens M, De Vet H, Van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International journal of technology assessment in health care. 2005;21(2):240–245.

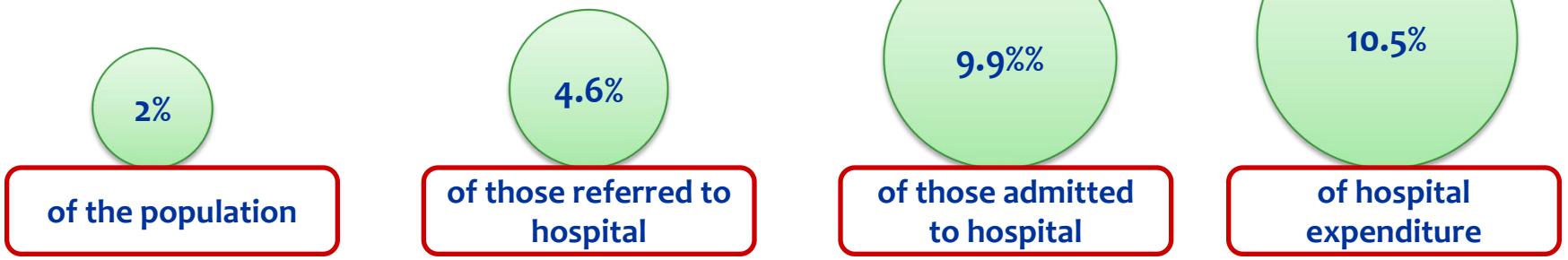
Despite some high costs, orphan drugs are generally affordable and cost-effective



Picavet E, Cassiman D, Simoens S. What is known about the cost-effectiveness of orphan drugs? Evidence from cost-utility analyses. Journal of Clinical Pharmacy and Therapeutics, 2015;(40(3)304-307.

Rare diseases have a disproportionately large impact on care utilisation and healthcare expenditure

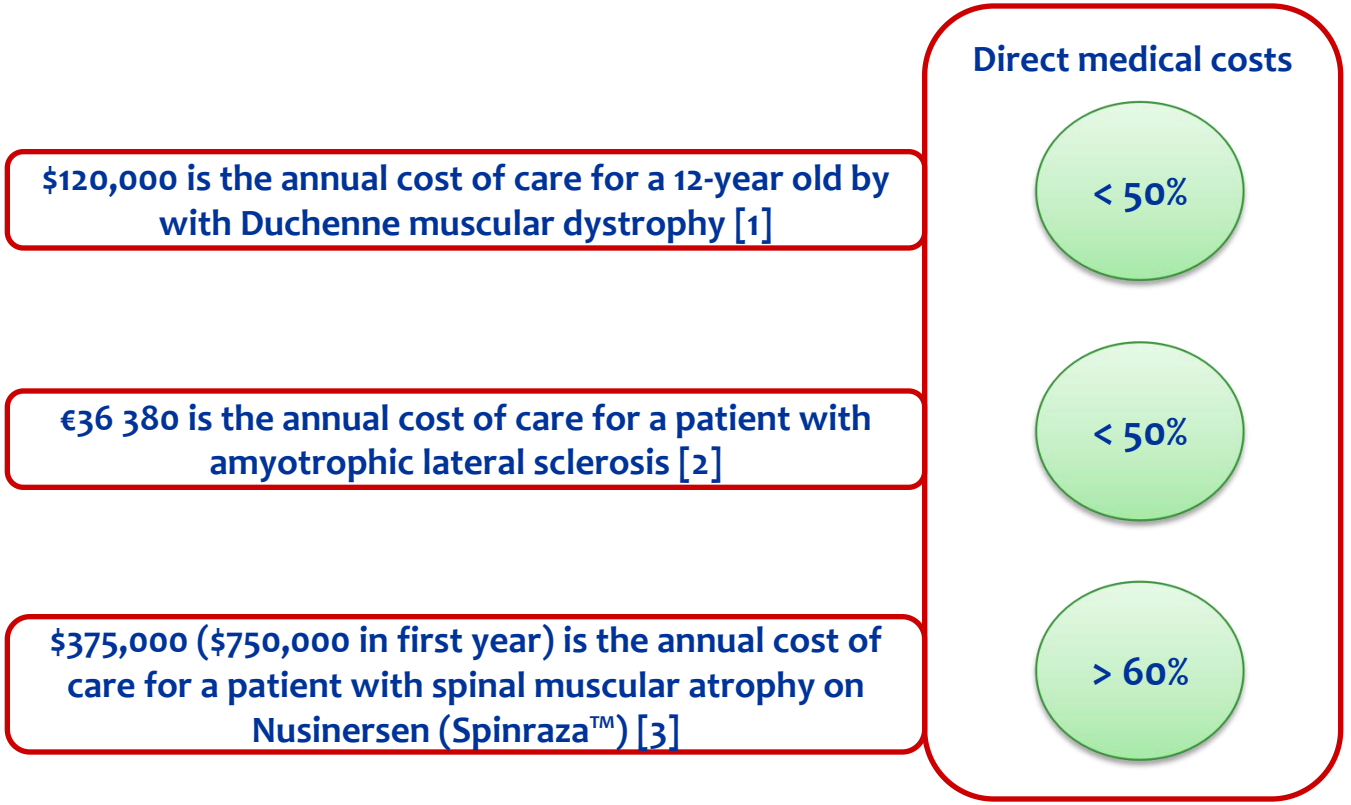
People living with rare diseases comprise ...



Consistent set of Australian data

Walker CE, Mahede T, Davis G, Miller LJ, Girschik J, Brameld K, et al. The collective impact of rare diseases in Western Australia: an estimate using a population-based cohort. Genetics in Medicine. 2017 May;19(5):546–52.

Cost burden associated with orphan drugs for rare diseases

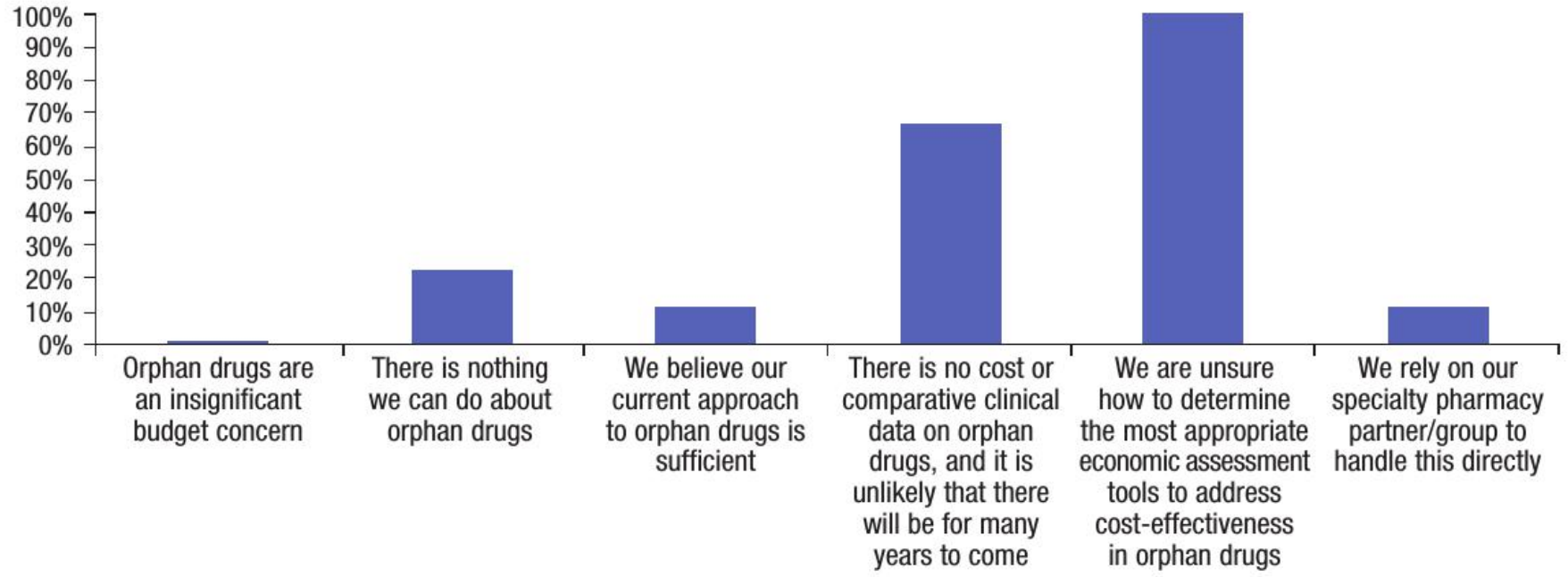


[1] Landfeldt E, Lindgren P, Bell CF, et al. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. Neurology. 2014;83(6):529-536.
[2] Elman LB, Stanley L, Gibbons P, McCluskey L. A cost comparison of hospice care in amyotrophic lateral sclerosis and lung cancer. Am J Hosp Palliat Care 2006; 23:212-216.
[3] Ollendorf DA, Chapman R, Pearson SD. Assessing the Effectiveness and Value of Drugs for Rare Conditions. Institute for Clinical and Economic Review. 2017.

Payers are confronted with difficult financial decisions when assessing orphan drug costs

Figure 6 Actions Taken for Orphan Drugs

Q: If you have no plans in place, what actions are you taking?



Signal

•[US] Payers express a high degree of uncertainty in assessing the cost/effectiveness of orphan drugs within budgets.

Handfield R, Feldstein J. Insurance companies' perspectives on the orphan drug pipeline. American health & drug benefits. 2013;6(9):589.