Rare Diseases

Digital Health Solutions*

We analysed over 8000 published Clinical Trial submissions that indicated a digital health componei corresponding to studies commencing from January 2010 to May 2021 to determine

- Focuses
- Solution creation as a function of the patient journey
- Solution classification related to regulatory definition
- Characteristics of evidence-based generation

They were screened, confirmed as digital health, sorted and analysed:
39 were focused on Digital Health Solutions for 24 different Rare Diseases

Despite the shortage of dedicated Rare Disease focused digital health solutions considering the greater than 7000 that exist, for innovators in this field, it is worthwhile to also consider the comorbidities of the rare disease, such as neurological, musculoskeletal, respiratory, mental health and cardiovascular.

Reviewing digital health solutions developed for these areas may identify potential 'digital health combinations' of packaged digital health solutions, or reveal existing solutions that could be edited, to provide a targeted benefit.

Study focus	Number of studies
Amyotrophic Lateral Sclerosis	4
Cerebral Palsy	2
Cleft Lip and Palate	3
Sickle Cell Disease	2
Neuromuscular Diseases (broad)	2
Cystic Fibrosis	2
Facioscapulohumeral Muscular Dystrophy	2
Myasthenia Gravis	2
Fabry Disease	2
Fragile X Syndrome (FXS)	2
Lupus	2
Blepharoptosis	1
Cervical Spondylosis	1
Down Syndrome	1
Dystonia	1
Erythema	1
Hallux Valgus	1
Marfan Syndrome	1
Progressive Supranuclear Palsy	1
Raynaud Phenomenon	1
Spinocerebellar Ataxia	1
Systemic Sclerosis	1
X-linked adrenoleukodystrophy	1
Wilsons Disease	1

*Methodology: The NIH clinical trial database was interrogated 3 independent times. Under the advanced search option, the first two search criteria were i) digital in other terms only for generic digital solutions that incorporated all diseases and ii) pathology in condition + digital in other terms. Recruitment terms were not yet recruiting, recruiting, enrolling by invitation, active not recruiting and completed. For each pathology this generated two data files, that after mining indicated keywords, that along with those obtained from our innovation briefings, were used in the third search to extend the data set beyond the major applications. This was performed identically to search ii) except the keyword was inserted in place of the pathology, thereby extending the data set extensively beyond the study focus, and also into other diseases. Dates of screening were for all clinical studies submitted up to May 24, 2021. For each search no geographic, lingual or digital solution constraint was used prior to generation of the data files. The three different data files were screened to confirm the health issue, a clear digital innovation (based upon peer reviewed literature sources such as Lancet Digital, Health Informatics Journal, Nature digital medicine, UK NICE, FDA, ICER, WHO). Each data file was then sorted to remove any duplicates and all remaining study files evaluated for key metrics including pathology, type of **Digital Health Solution**, primary purpose within **the Patient Journey** and suballocation.*

Ethics: Patient metric mining and mHealth

'If you are not paying for it, then you're not the customer; you're the product being sold'

Tim O'Reilly 2010, crediting Andrew Lewis

Ethical management in digital health has mainly focused on privacy, security, equality, accessibility and data protection. A developed solution once it addresses these issues, is considered legitimate; breaches result in fines and possible criminal charges. However, it then enters a concept of data usage that has been best presented in '*The Age of Surveillance Capitalism: The fight for a human future at the new frontier of power*' by Professor Shoshana Zuboff. What we can now find in digital health are free mHealth solutions (clinically validated through observational trials, or not) that enable a direct interaction between a patient and their health care professional (P-HCP). P-HCPs are not the same as Electronic Health Records, that at a minimum always require informed consent for data sharing, and in many cases are legislated for.

P-HCPs will facilitate increased disease knowledge, communication and higher quality care: enabling remote symptoms reporting, treatment monitoring and adherence, and wellbeing assessment. The patient's privacy is respected as their data is anonymised; however, the Terms and Conditions of the solution can vary between P-HCPs, with some indicating all the data, while developed and obtained by one entity, actually belongs to or is accessed by another entity that has paid for the P-HCPs development. This anonymised data is very valuable.

Applicable to all diseases, it is most clearly illustrated in rare diseases. Insufficient funding for fundamental and clinical research for patients with rare diseases means that large scale clinical data sets do not exist: the rare nature of the disease also means that there are very few patients from which to generate statistically relevant information. This makes it difficult to demonstrate clinical efficacy or Treatment Outcome of any health solution, and thus pass the first regulatory hurdle of national or trading bloc market approval.

To address this there is an increasing usage of Patient Reported Outcomes (PROs) as Treatment Outcome measurements for rare diseases (and for common diseases that use personalised solutions). PROs, used in routine patient management, enable patients to tell the healthcare professional how they feel using Patient Reported Outcome Measures (PROMs): these validated questionnaires exist for major diseases and indicate functionality, quality of life and symptom, but not clinical, manifestation. Generic examples include the EQ-5D: https://euroqol.org/eq-5d-instruments/sample-demo/, cancer specific types can be found at https://qol.eortc.org/questionnaires/, for rare diseases, some exist but independent development is needed for many of them, and are ongoing for some, such as Duchenne Muscular Dystrophy.

PROs generated via PROMs are also used by reimbursement agencies (CADTH, NICE, PBAC) to perform calculations through HEOR modelling to evaluate solution cost-utility (QALY, quality adjusted life years measurements; BIA, budget impact analyses), and determine if and how much should be paid for the solution.

P-HCP mHealth solutions, can mimic PROs, enabling entities that collect or have access to the anonymised patient data to gain unparalleled and unfettered knowledge of the patient treatment, test outputs, their wellbeing and how they feel: patient metric mining. This has the potential to create bias: it can enable the data owners to generate PROs and PROMs that favour a specific solution, making it appear it is better versus a competitor that is on the market or in development. This has huge value for companies.

For example, a selected patient population manifests a patient metric output with one entities intervention, when compared to another's, that is identified through P-HCP communication. A PRO is then generated or adapted that includes the question 'how do you feel after treatment regarding symptom metric X?'. This can influence the utility calculation making one entities solution automatically look more valuable than another's; without any evident clinical change or benefit to the patient.

Some will argue that this does benefit the patient: but then more transparency on what the data is used and can be used for, may be necessary. Observational clinical trials can be exempted from informed consent requirement if the Institutional Review Board perceive the solution as minimal risk for the patient, which many mHealth solutions are, but what the data could be used for, and by whom, may be obscured.

It may be advisable that all P-HCP mHealth solutions that collect any patient data should be accompanied by an obligatory and explicit informed consent form detailing what the data will be used for, by whom and for what end, as for other patient samples. Otherwise, while these solutions may well be legal, it begs the questions, who is really benefitting and is it ethical?

The Patient Journey* & Digital Health Solutions

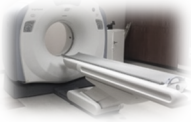
Health Services

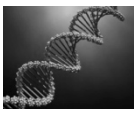
Symptoms awareness and monitoring

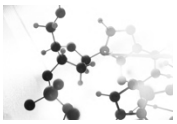
Family Healthcare Practitioners (FHP)
First evaluation

Population Health Dynamics:
Screening of at-risk populations

Secondary and Tertiary care specialists
Diagnosis: confirmation and definition







Outpatient or Tertiary care
Treatment and supportive care

Successful treatment

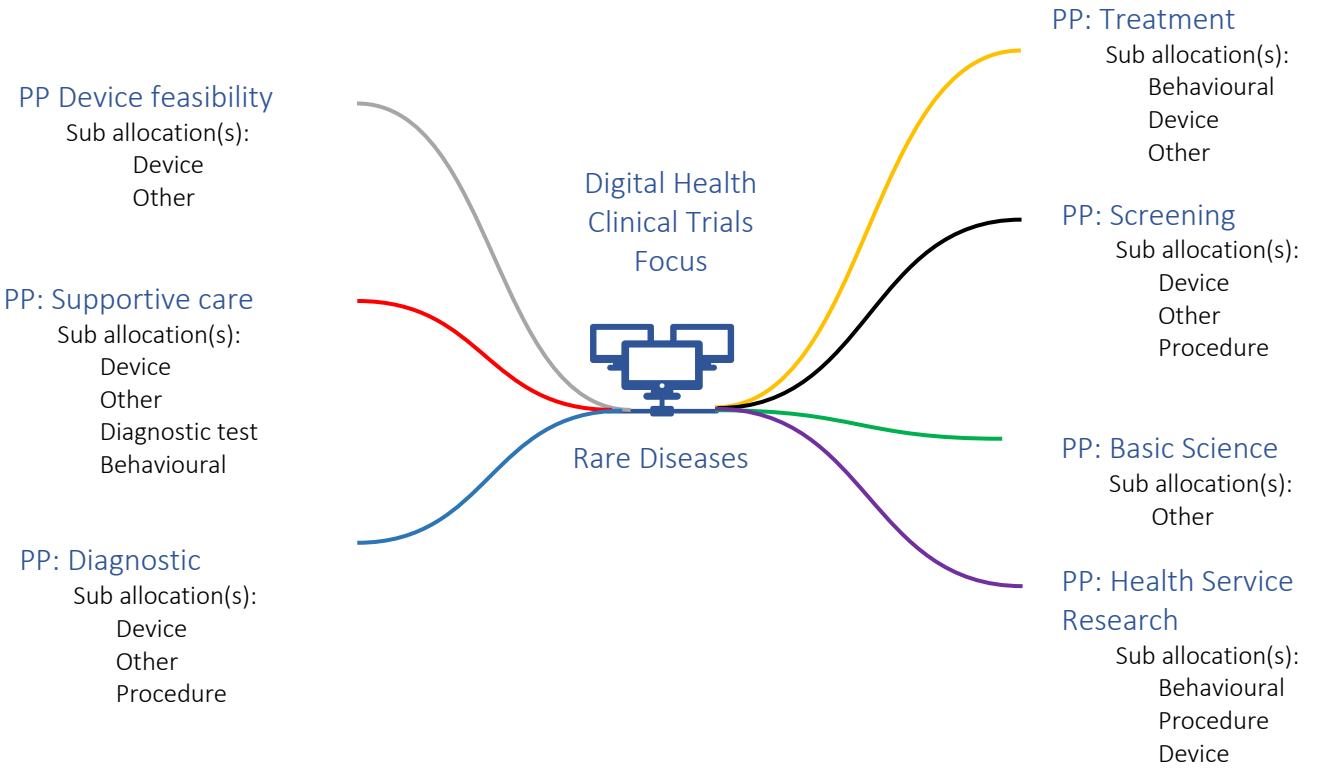
Relapse monitoring

Outpatient or FHP
Supportive Care, Follow up +/- specialised clinics
(Mol. Diag. Labs/Imaging clinics)

*(*low granularity)*

Digital Health Solution Classifications

Digital Health Solutions have been focused around 7 Primary Purposes (**PP**) with up to 4 different suballocations depending on what it is, where it will have an impact and outcome measures to confirm it.



Each country has its own digital health framework and strategy, and classification and evidence requirements. Global Healthcare payment typically falls in the spectrum from Majority publicly to Majority privately funded. But there is also the system where no structured healthcare exists at all, whose people need healthcare the most; using this spectrum while integrating the stakeholders needs in each location, we can assess clinical and economic evidence needs, and how to generate data that best demonstrates the solutions beneficial impact.

- Clinical Trial Design
- Clinical Efficacy requirements
- Health Economic Evidence needed

Clinical trial details by primary purpose and sub allocation for Rare Disease focused digital health solutions

Primary Purpose	Sub Allocation	Clinical Trial structure(s) followed	Median number of patients per trial	Median duration of each trial (months)*
Device feasibility	Device	Single Group Assignment	15	0.6
	Other	Single Group Assignment	15	6
Screening	Device	Single Group Assignment	50	0.2
	Other	Randomised Parallel	152	0.1
	Procedure	Single Group Assignment	270	0.1
Health service Research	Device	Non-Randomised Parallel	750	60
	Behavioural	Non-Randomised Sequential	368	6
	Procedure	Randomised Parallel	88	12
Basic Science	Other	Sequential Assignment	1040	4
Diagnostic	Device	Single Group Assignment	21	0.1
	Other	Single Group Assignment	100	0.1
	Procedure	Single Group Assignment	33	36
Supportive Care	Diagnostic	Cohort	160	18
	Device	• Single Group Assignment • Randomised Parallel • Cohort	33	7
	Behavioural	Randomised Parallel	60	6
	Other	• Cohort • Case-Only	68	2
Treatment	Behavioural	Randomised Parallel	40	5
	Other	Randomised Parallel	106	2
	Device	• Single Group Assignment • Randomised Parallel	60	1

**It is worthwhile reading the increasing number of reports and guidance documentation being produced by global reimbursement bodies regarding expert opinion on clinical trial duration and structure. The increasing trend of expert critique corresponds to the absence of long-term modelling of the impact of the solution vs the standard of care within a non-biased clinical design, that prevents accurate effectiveness analysis being performed.*

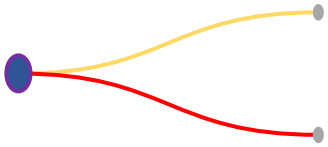
Solutions developed for Rare Diseases

Amyotrophic Lateral Sclerosis
n=4

Diagnostic
Device: Pressure meter

Supportive care
Device: Brain-Computer interface; pressure meter

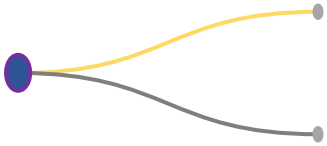
Cerebral Palsy
n=2



Treatment
Behavioural: Computerised functions

Supportive care
Device: Digital rehabilitation

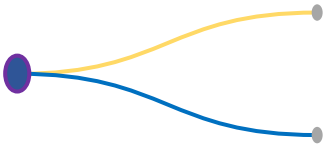
Cleft Lip and Palate
n=3



Treatment
Other: Planning software for surgery

Device feasibility
Device: Molding device Imaging

Neuromuscular (broad acting)
n=2



Treatment
Device: Brain-Computer interface

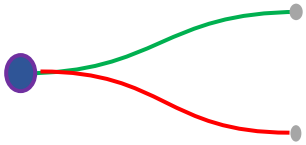
Diagnostic
Other: Digital play module for motor function assessment

Cystic Fibrosis
n=2

Health Service Research
Procedure: Home monitoring

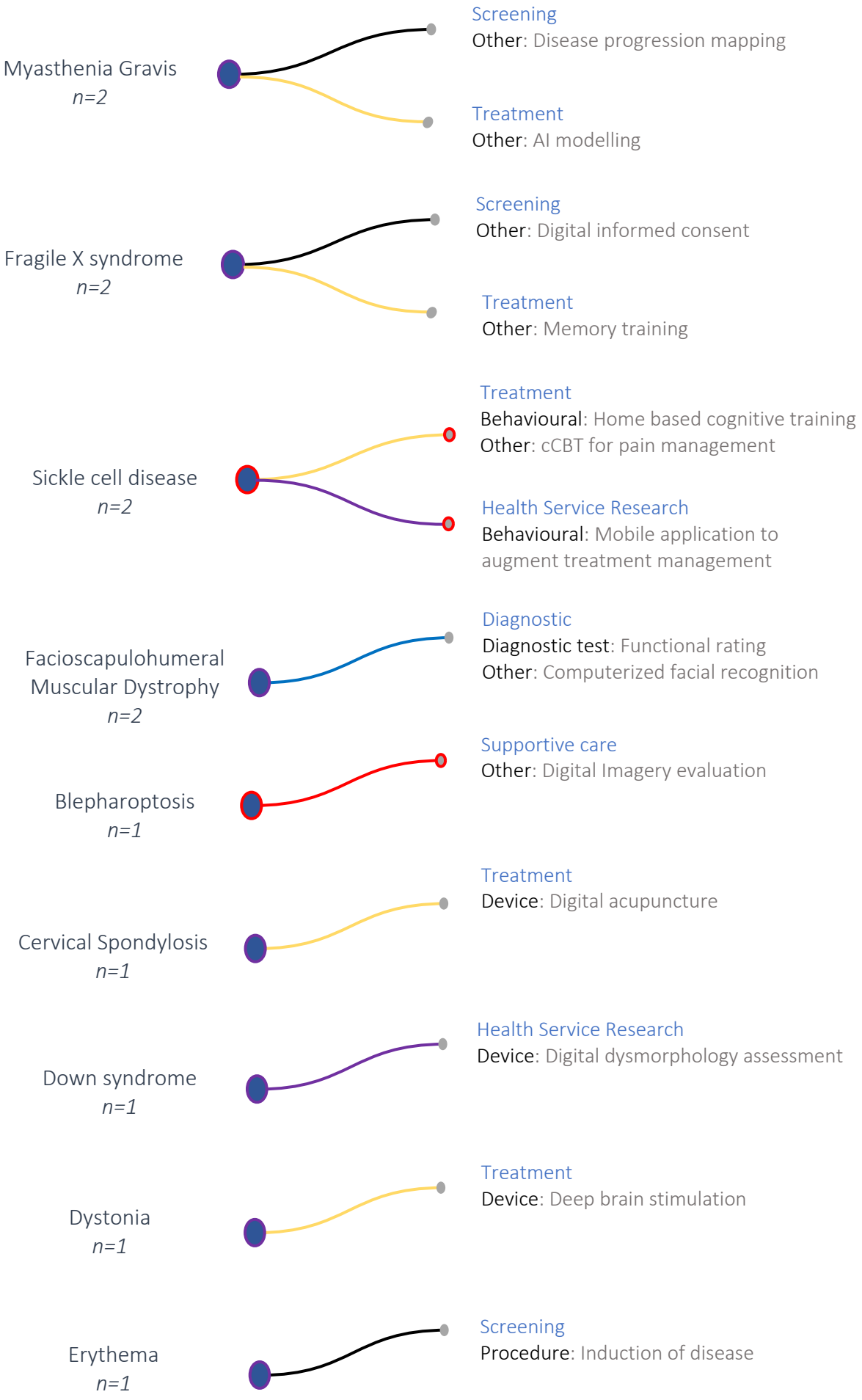
Device feasibility
Device: Wearable device

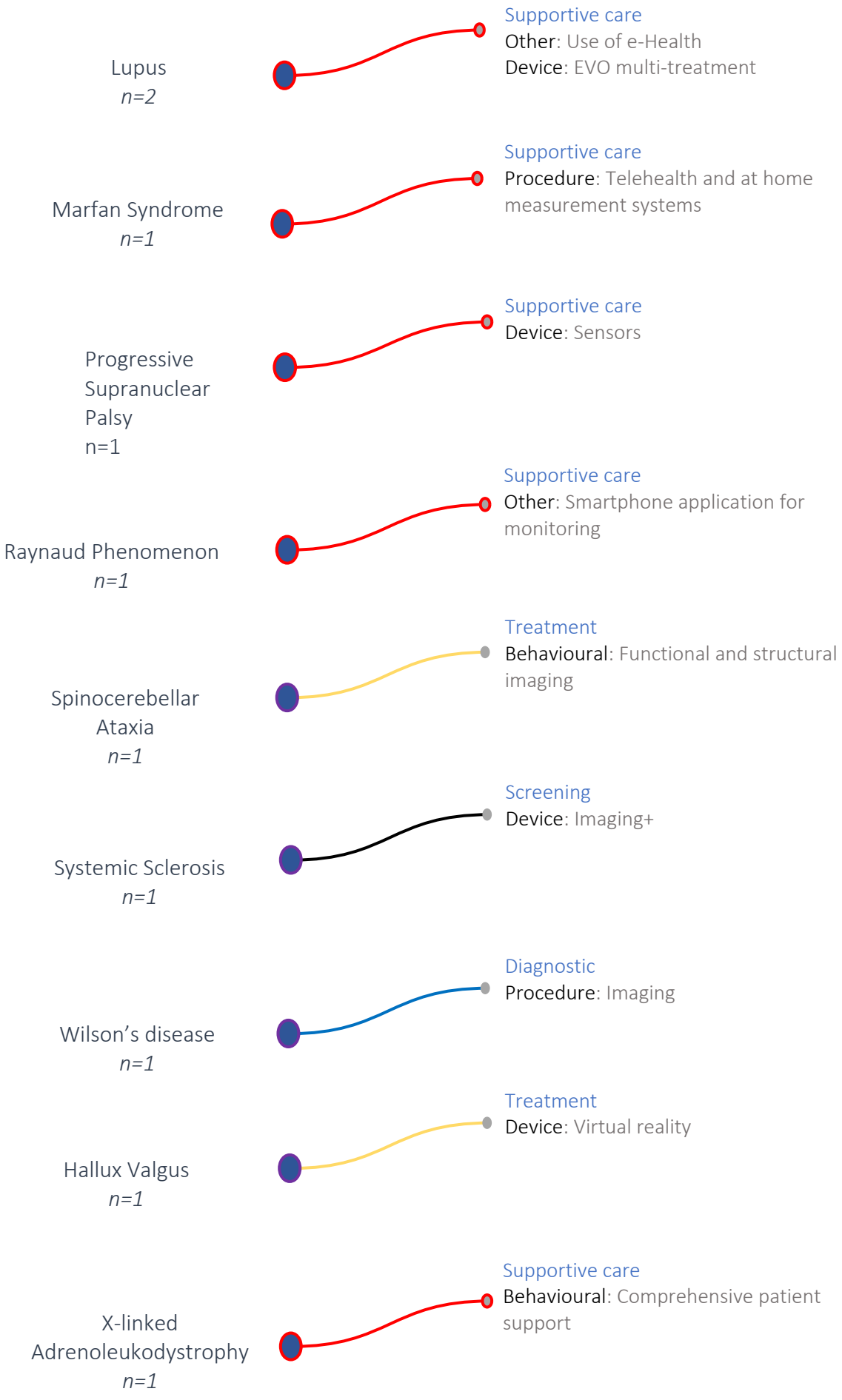
Fabry Disease
n=2



Basic science
Other: fMRI methods for white matter changes

Supportive care
Other: Zamplo





Valuations and solution vs stakeholder integration.

We have not included estimated market values or potential forecasts: the market is so fragmented that for every assumption why a value calculation variable should be fixed to permit value outcome modelling, there were (and are) a dozen confounders that rendered the calculation unreliable. More importantly because of the nature of rare diseases and how diagnostics and therapeutic solutions are lacking, this is a field where philanthropic endeavour to provide solutions at no cost but requiring investment could have significant impact. The recent pandemic may have illustrated to the public that for those with rare diseases our frustration of not being able to easily leave our abodes, is for them is often a daily occurrence, and its lifelong.

Typically, value calculations are based upon an as precise as possible defined population, using that solution. This is then stratified by population health dynamics, where in the healthcare work flow it has relevance and what it is doing: study focus vs patient journey location vs patient population it is designed for vs classification vs primary purpose.

People with rare diseases do not have that benefit: entities such as NORD, OrphaNet, and the numerous groups, patient associations (PA) and charities or doing their utmost to provide solutions and insights through continental and global networking, but for budding digital health entrepreneurs this maybe one field where digital solutions, that enable an easier global solidarity, health care specialist education, networking, carer/parent support for each rare disease would raise the bar and enable the supporting entities to have an ever greater impact, providing all the data remains the property of the patient and is governed by a PA.

Evidence bases for economic or health impact of the majority of digital health solutions are unestablished, and from our analysis there are significant and positive motivations, and amounts of effort being engaged to generate them, in rare diseases, there are clearly not enough; in general there are still some critical aspects not being considered, that includes full stakeholder involvement. Best illustrated by the increasing numbers of peer reviewed publications authored by healthcare workers for mHealth apps that follow a work flow of:

> *'Based on pathology A, we searched the google and apple stores for solutions linked to it. 249 applications were identified, that after a sorting algorithm corresponding to actual patient healthcare measurement metrics, 9 merited in depth analysis to assess if they had been generated on an evidence base, of which 2 actually did what it said on the box'.*

Design and functionality considerations

Clinical trial design

Make sure it is of the highest quality including the necessary patient numbers for a valid power calculation. A typical solution requires over 1000 patients to demonstrate an effect if the difference between positive and negative is significant with a 90% power: if the difference is small, over 6000 patients are normally needed.

Clinical trials performed in different settings, with different healthcare practitioners, on different populations and in different scenarios result in non-comparable data obfuscating the value.

Total inclusion of evidence and regulatory requirements

So far, many solutions are revealing that clinical trial data vs real world setting outcomes and data are not correlating during post marketing assessments: in most cases the real world data is indicating that the clinical trial data was optimistic.

The solution needs to be positioned with the most relevant healthcare worker in the most pertinent location to identify, clarify and emphasise the value. There also may be the need for routine and continued education of the patient and healthcare workers to maintain impact of the solution.

With regards to Artificial Intelligence and Machine Learning Algorithms the integrity and completeness of training and validation data sets can influence and, in some cases, have been shown to increase healthcare provision disparity.

Healthcare practice location usage and available infrastructure

A family doctor, specialist nurse or hospital physician using the same solution on the same patient can generate data variations: this creates confusion, which most healthcare workers do their utmost to avoid.

This can create stakeholder misalignment: conflicting stakeholder opinions creates subjective norm barriers. Stakeholder requirements need to be integrated into your solution design: remember that the healthcare worker has to approve, prescribe or recommend the solution.

Interoperability with various EHRs or other IT solutions typically used in that specific geography, are still an issue, resulting in poor conceptual integration of solution into healthcare delivery workflow that is still occurring.

Integrate total system, pathway or workflow impacts and Total Costs of Ownership when costing your solution: no customer likes a surprising bill.

The solution is difficult to roll out: needs specific infrastructure and trained personnel.

IT connectivity: The GSMA 2020 report on mobile internet connectivity indicates that only 600 million people live in areas with no connectivity; but nearly half the world's population, despite living in areas with a mobile broadband network do not use mobile internet. Lack of digital skills, computer literacy and device/data plan affordability represent barriers to usage.

There is also a significant gender gap on mobile internet usage, biased against women, that is geography dependent, with a higher relevance in LMIC geographies. We need to reprioritise.

Accuracy, sensitivity and specificity is everything

Contradictory diagnosis is a problem: if the output data does not correlate with existing standards of care or gold standard approaches health care workers will have justifiable doubts: the buck stops with them. Remember that this has geographic relevance: different thresholds in different countries influence application and accuracy assessments, that can hinge on healthcare worker education.

In every country evidence of misdiagnosis is fatal: false positives and false negatives, true positives and true negatives define every intervention: Diseases getting missed, or incorrectly diagnosed can result in no treatment or unnecessary surgery and treatment. No stakeholder wants that.

Understand the patient

This needs to be long-term and educational. Poor understanding of enduser(s) needs and level of involvement can sink your solution at the post market level. Some patients do not want to be constantly reminded they are ill.

Lack of consideration for impacts of income level, age, ethnicity or gender will result in bias or health disparity: Lack of integration of normal human behaviour or disease characteristics such as comorbidities will reveal inherent design weaknesses that will only occur when a practicing specialist committee reviews the data.

Understand the healthcare worker

There are insufficient numbers of healthcare staff in every location: Low number of healthcare workers vs high patient load routinely creates message over saturation, 'alert or alarm' fatigue, mental overload, decreased situation awareness, resulting in incorrect decisions. Make sure your solution is not just creating a different problem.

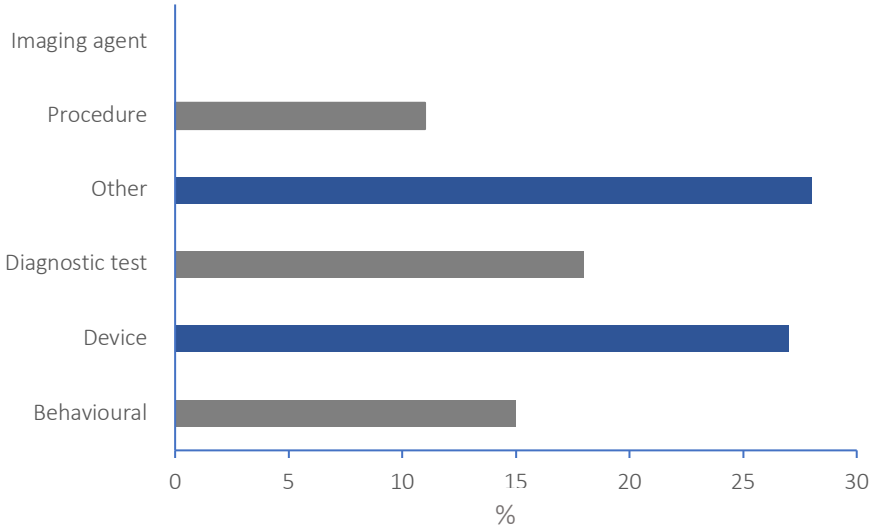
Do you understand the enduser(s) time constraints and decision making as a function of where they work in the healthcare ecosystem?

Healthcare workers are not IT specialists: they have IT management, IT security and privacy issues. Many healthcare workers have to buy their own IT solutions without knowing IT issues related to security, software and operating systems. If your solution fails and there is patient harm via health damage or data breach, they are likely liable. A nice GUI is always reassuring, but the problem is not there. Healthcare workers need tailored IT training that corresponds to real world needs and their availability.

Annex: Trend analysis

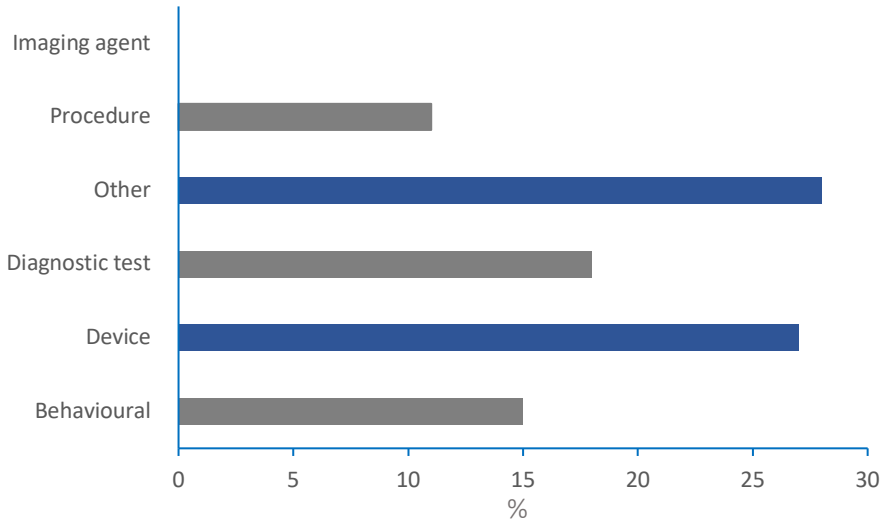
Screening over 8000 files provided a unique opportunity to also look at trends: digital health solutions do not go through the same trial phases as therapeutics and by being performed in accredited healthcare settings trend analysis gives a view of what solutions healthcare specialists and Key Opinion Leaders think are the best to try and the most necessary for each work flow focus and the patient.

Screening: major solutions groups and types



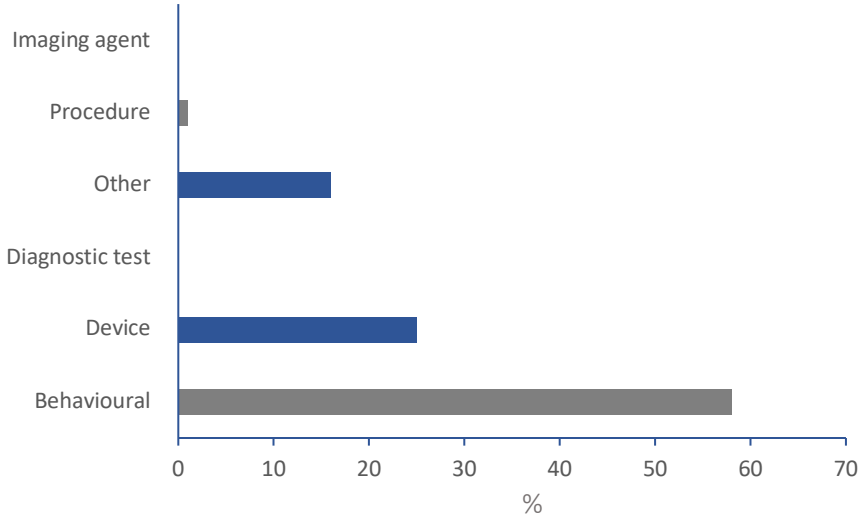
- Behavioural: raising awareness of the potential for the disease
- Device: almost 100% new imaging approaches within existing work flows
- Diagnostic test: almost 100% application of existing imaging platform and imaging optimisation within existing work flows or mobile imaging +/- telemedicine
- Other: genetics, online questionnaires, family gene toolkit, fecal occult blood test
- Procedure: introduction of imaging into existing workflows

Treatment: major solutions groups and types



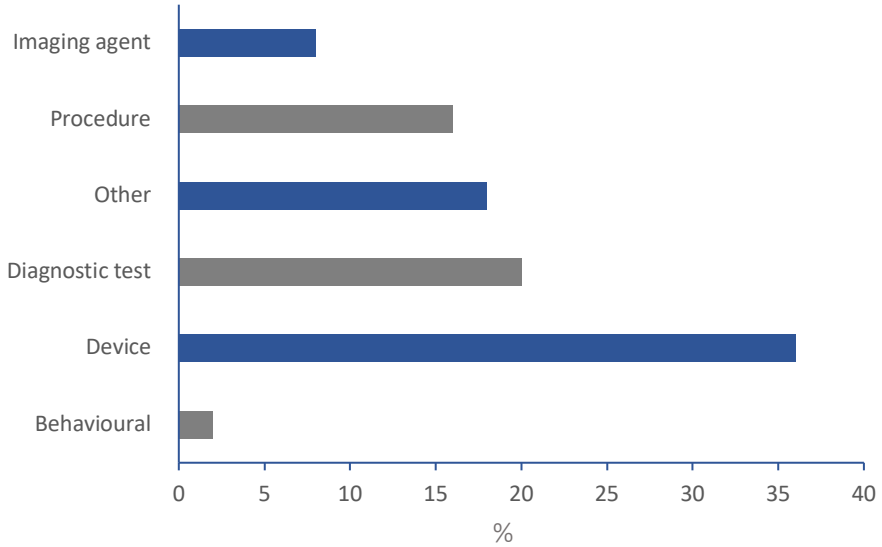
- Behavioural: guides, counselling, education, telemedicine, sensor+app, communication solutions, ePillbox, gaming, cognitive support through all informatic platforms
- Device: virtual reality, gaming solutions, hand held stimulation devices, mental rehabilitation through mHealth, every type of informatic platform rehabilitation
- Other: virtual reality solutions, app/mobile/tablet cognitive therapy, musical solutions
- Procedure: drug monitoring/adherence, digital subtraction angiography, deep brain stimulation, telemedicine

Prevention: major solutions groups and types



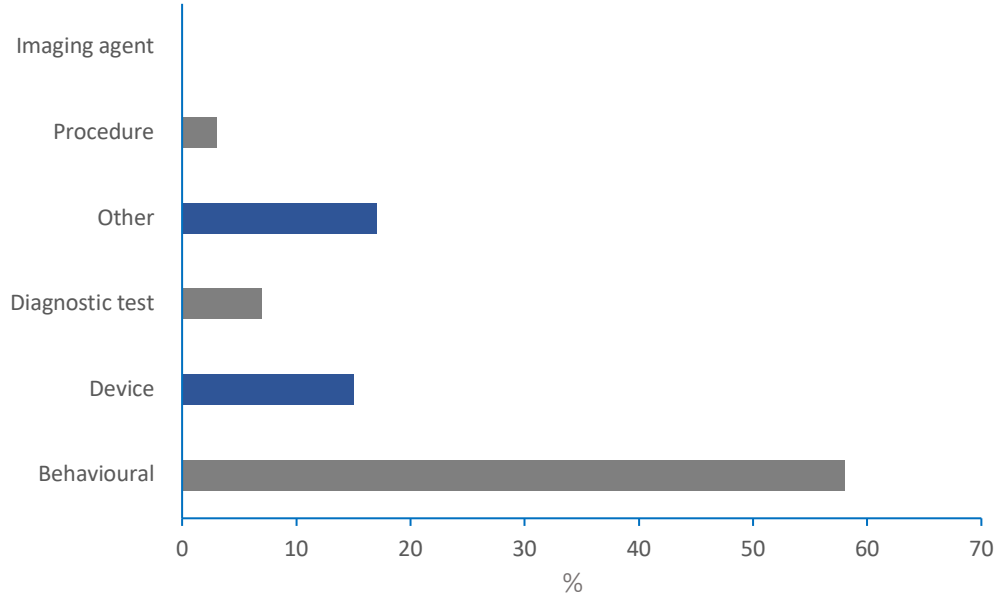
- Behavioural: tele-education, tele-counselling, virtual reality, augmented reality, apps and mHealth +/- activity training/augmentation, online cognitive training,
- Device: sensors, sensor+app, home based comprehensive solutions, mobile imaging
- Other: smartHealth solutions, gaming, apps, messaging, cognitive training
- Procedure: connected informatic solutions

Diagnostic: major solutions groups and types



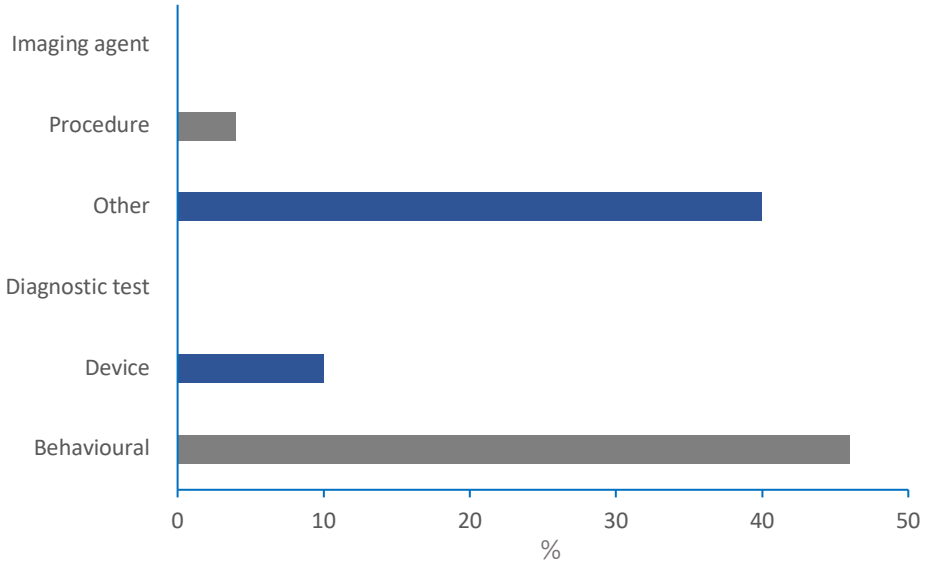
- Behavioural: cognitive questionnaires
- Device: imaging, sensors, monitoring systems, gaming, cognitive evaluation
- Diagnostic test: imaging, sensors, sensor+app, cognitive assessment, virtual biopsy/digital biomarker
- Drug: imaging agents
- Other: apps, augmented reality, AI, mental health questionnaires
- Procedure: mostly imaging related

Basic science: major solutions groups and types



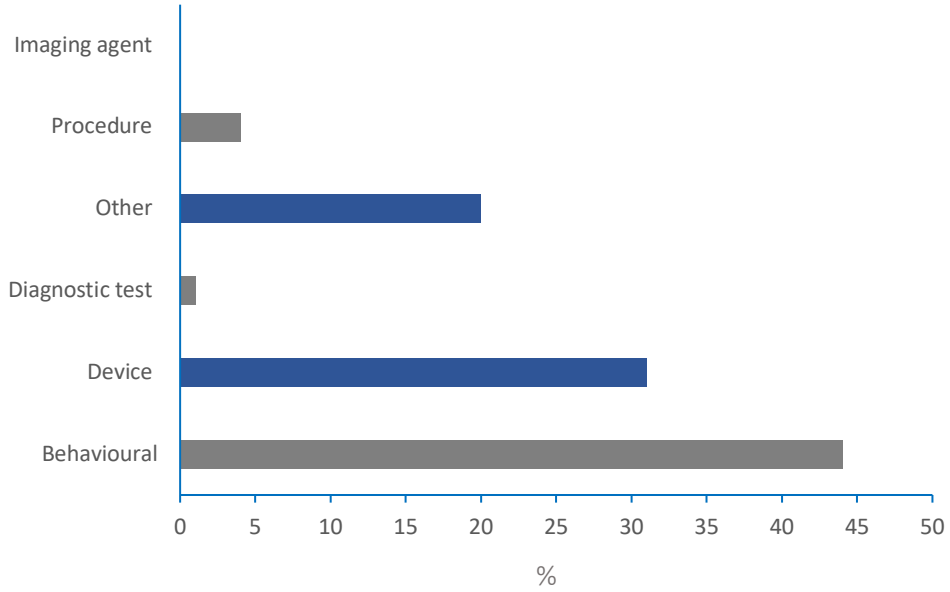
- Behavioural: music, apps, gaming, exergaming, physical/diet changes
- Device: sensors, monitors, ehealth, electrical stimulation, wearables
- Diagnostic test: imaging
- Other: imaging, sensors, music
- Procedure: electrical stimulation

Health service research: major solutions groups and types



- Behavioural: self-management solutions, education, counselling, sensors, PROM/symptom reporting, physical activity encouragement, virtual reality, mental health support
- Device: gaming, cognitive aids, sensor/phone+app
- Other: integrated mHealth, virtual reality, telemedicine, home based monitoring and sensors
- Procedure: home monitoring, telemedicine

Supportive care: major solutions groups and types



- Behavioural: counselling, education, apps, mHealth, sensors, gaming, activity support, self management, cognitive support, mental health support
- Device: sensor/smart device+app, smart device+new sensor, physical activity support and tracking, virtual reality, self care, telemedicine, telemonitoring,
- Diagnostic test: imaging
- Other: imaging, eHealth platforms, at home sensors/monitoring+/- apps,
- Procedure: gaming, home monitoring

About Echino Limited: an internationally focused programme management and medical communications company that specialises in global programme management and convergent technology project implementation, with a particular focus on optimising operations.

About the author: Dr. Jonathan Dando has approaching 30 years global insight in life science and health, with work experience in Austria, the United States, Italy, France, Switzerland, the UK and Spain. He started his career in the early 90's working in Gene Therapy for Novartis and SyStemix (USA), has held academic positions in Foundation and National research institutes, including TIGET and Inserm, as well as Executive Directorships and Board positions in commercial enterprises, some of which he started. Since 2002 he has specialised in aiding, designing and managing international research, development and clinical trial partnerships and alliances between all stakeholders and actors, in which he has also raised over €150 Millions, and in helping private foundations with their international projects. He has an Honours Degree in Biophysics and a PhD in the Genetic Engineering of Viruses; he also holds a micro masters in Cloud computing, has been trained as a Facilitator for the UK NICE's Medtech Early Technical Assessment system, and also acquired several continuing professional education certificates in clinical trial design, health technology assessment, eHealth, population health and data management.

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