THEMATIC ANALYSIS OF TECHNOLOGY APPRAISALS WITH LARGE ESTIMATED QALY GAINS

REPORT BY THE DECISION SUPPORT UNIT

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Author, Lesley Uttley[1]

[1]School of Health and Related Research, University of Sheffield

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street
Sheffield, S1 4DA

Tel (+44) (0)114 222 0734
E-mail dsuadmin@sheffield.ac.uk
Website www.nicedsu.org.uk
Twitter @NICE_DSU

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EXECUTIVE SUMMARY

This report presents a thematic analysis of twenty-two completed NICE appraisals that have been identified as likely to produce large QALY gains (defined as ≥2 QALYs gained). The purpose of the work was to identify common characteristics that potentially underpin the large QALY gains, estimated from the cost-effectiveness analyses of the technologies reviewed, which could be used to identify technologies in the early stages of development with high potential to deliver major improvements in health outcomes in the future.

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ABBREVIATIONS AND DEFINITIONS

AAC	Accelerated Access Collaborative
DSU	Decision Support Unit
ERG	Evidence review group
HCV	Hepatitis C virus
HST	Highly specialised technology
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
QALY	Quality-adjusted life year
ScHARR	School of Health and Related Research
SoC	Standard of care
STA	Single technology appraisal
TVP	Therapeutic value proposition

1. INTRODUCTION

1.1. BACKGROUND

The National Institute for Health and Care Excellence (NICE) makes decisions about which novel health technologies will be funded and adopted by the National Health Service (NHS). The effects of these decisions can displace resources that were previously assigned to other interventions and patient groups but can also encourage further investment and promote innovation in future health technologies. The Accelerated Access Collaborative (AAC) aims to support products with high potential to speed up access to these health technologies for patients. These products are expected to offer large health benefits (defined as ≥2 quality-adjusted life years (QALYs) gained). To support the work of initiatives aimed to expedite the approval, reimbursement, and adoption of promising new technologies such as the AAC it is important to understand the range and nature of features that can identify technologies that may be capable of producing large health-related benefits to patients.

1.2. OBJECTIVE OF THIS REVIEW

The aim of this work was to examine characteristics of health technologies which the NICE appraisal process has previously deemed as likely to produce substantial QALY gains and to draw inferences from common themes which may underpin the technology's or the decision problem's potential to deliver large health-related benefits in the future. The definition of technologies with high potential to deliver major improvements in health-related outcomes for the purposes of this review was an expected mean QALY gain of two or more. The objective is to inform a framework to make the process of assessing early stage products against set eligibility criteria more systematic and objective.

1.3. RESEARCH QUESTIONS

1. Do technologies that have demonstrated two QALY gains or more in published NICE guidance have common features that can be used to identify early stage technologies with the potential to deliver major improvements in health outcomes?

2. Can the same inference be made for diagnostic tests and medical devices given that medical technology evaluations focus more on cost minimisation and diagnostic assessments rarely record significant benefits with guidance usually being cost incurring.

2. METHODS

2.1. IDENTIFICATION OF RELEVANT NICE APPRAISALS

A mixed approach was taken for obtaining relevant appraisals:

1. The DSU at ScHARR searched NICE technology appraisals undertaken between 2011 and 2015 in an unrelated project, where the submissions were examined in order to identify the incremental QALYs gained. Twelve appraisals identified from this work were identified as relevant due to estimating 2 or more QALYs gained.
2. NICE identified appraisals with large QALY gains that took place between 2015 to 2018 and provided a list of these to the DSU at ScHARR. These appraisals include highly specialised technology (HST) appraisals whilst DSU work did not. Ten further appraisals were identified by NICE in this manner.

Overall, twenty-two relevant appraisals identified as having large QALY gains were used to inform this work. All were NICE technology appraisal or HST appraisals.

2.2. INFORMATION SOURCES

Documentation published on the NICE website were primarily used to extract data to inform the review. This included:

- Final NICE scopes
- Company evidence submissions
- Evidence review group (ERG) reports
- Final appraisal determinations (FAD)

As academic or commercial in confidence data were redacted in the documents available on the NICE website, *PharmacoEconomics* journal publications of the ERG perspectives on NICE STA processes were occasionally sought to verify if redacted data had subsequently become publicly available and was used to extract data for this report.

2.3. DATA EXTRACTION

Key information from each appraisal were extracted into an Excel worksheet including:

- The type of technology and mechanism of action

- The target patient population/condition
- The comparator/current standard of care (SoC)
- Estimated quality of life for SoC
- Therapeutic value propositions (TVPs) proposed by the company
- NICE appraisal committee discussion regarding the innovative nature of the technology.

2.4. DATA SYNTHESIS

A two-stage approach was taken to identifying themes that could indicate technologies with potential to provide distinctive benefits of a substantial nature:

i. Appraisals were assessed for common characteristics in order to draw out themes relating to the technologies or decision problems that potentially underpin the large QALY gains.

ii. Qualitative analysis was undertaken to identify common qualitative themes which transpire through the technology appraisal process that potentially underpin the large estimated QALY gains.

Items generated from the thematic analysis were organised into a framework of over-arching domains that capture the essence of each theme. Themes were coded and codes were re-applied to the extracted data to display the commonality of concepts among and between appraisals.

3. RESULTS

3.1. CHARACTERISTICS OF INCLUDED APPRAISALS

The 22 NICE appraisals for technologies identified as producing QALY gains of 2 or more are described in Table 1. As NICE single technology and HST appraisals do not cover diagnostic tests or medical devices, all technologies identified were medical interventions.

Table 1. Characteristics and range of appraisals, ordered chronologically

Intervention **NICE ID (Year of appraisal)**	**Condition**	**Intervention type** **Mechanism of action**	**QALY gain**
Bosutinib TA401 (2013)	Previously treated (1 or more tyrosine kinase inhibitor) chronic, accelerated and blast phase Philadelphia chromosome positive chronic myeloid leukaemia in adults	Drug (oral) Second Generation- "BCR–ABL/SRC" tyrosine kinase inhibitor	4.8
Sofosbuvir TA330 (2015)	Chronic hepatitis C (genotypes 1, 3, 4, 5 & 6)	Drug (oral) Uridine nucleotide analogue inhibiting hepatitis C virus (HCV) polymerase	2.1 to 2.6
Ledipasvir-sofosbuvir TA363 (2015)	Chronic hepatitis C (genotypes 1 & 4)	Drug (oral) HCV NS5A inhibitor and nucleotide analogue inhibitor of HCV NS5B polymerase	4.7
Ombitasvir-paritaprevir-ritonavir with or without dasabuvir TA365 (2015)	Chronic hepatitis C (genotypes 1 & 4)	Drug (oral) Combines direct-antivirals to target and inhibit specific HCV proteins from replicating	2 to 2.2
Eculizumab HST1 (2015)	Atypical haemolytic uraemic syndrome	Drug (intravenous) Monoclonal antibody to complement C5, which blocks pro-thrombotic and pro-inflammatory processes	10.14
Elosulfase alfa HST2 (2015)	Mucopolysaccharidosis type IVa	Drug (intravenous) Recombinant form of human Nacetylgalactosamine-6-sulfatase	10.03
Nivolumab TA384 (2016)	Advanced (unresectable or metastatic) melanoma	Drug (intravenous) Human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1)	3.08
Ruxolitinib TA386 (2016)	Disease-related splenomegaly or symptoms in adults with myelofibrosis post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis in people with intermediate-2 or high-risk disease.	Drug (oral) Protein kinase inhibitor that targets Janus associated kinase (JAK) signalling	4.8
Lumacaftor-ivacaftor TA398 (2016)	Cystic fibrosis homozygous for the F508del mutation	Drug (oral) Systemic protein modulator, corrector of the cystic fibrosis transmembrane conductance regulator (CFTR)	3.45
Elbasvir-grazoprevir TA413 (2016)	Chronic hepatitis C (genotypes 1 & 4)	Drug (oral) Disrupts HCV NS5A replication by inhibiting key HCV proteins	2.074

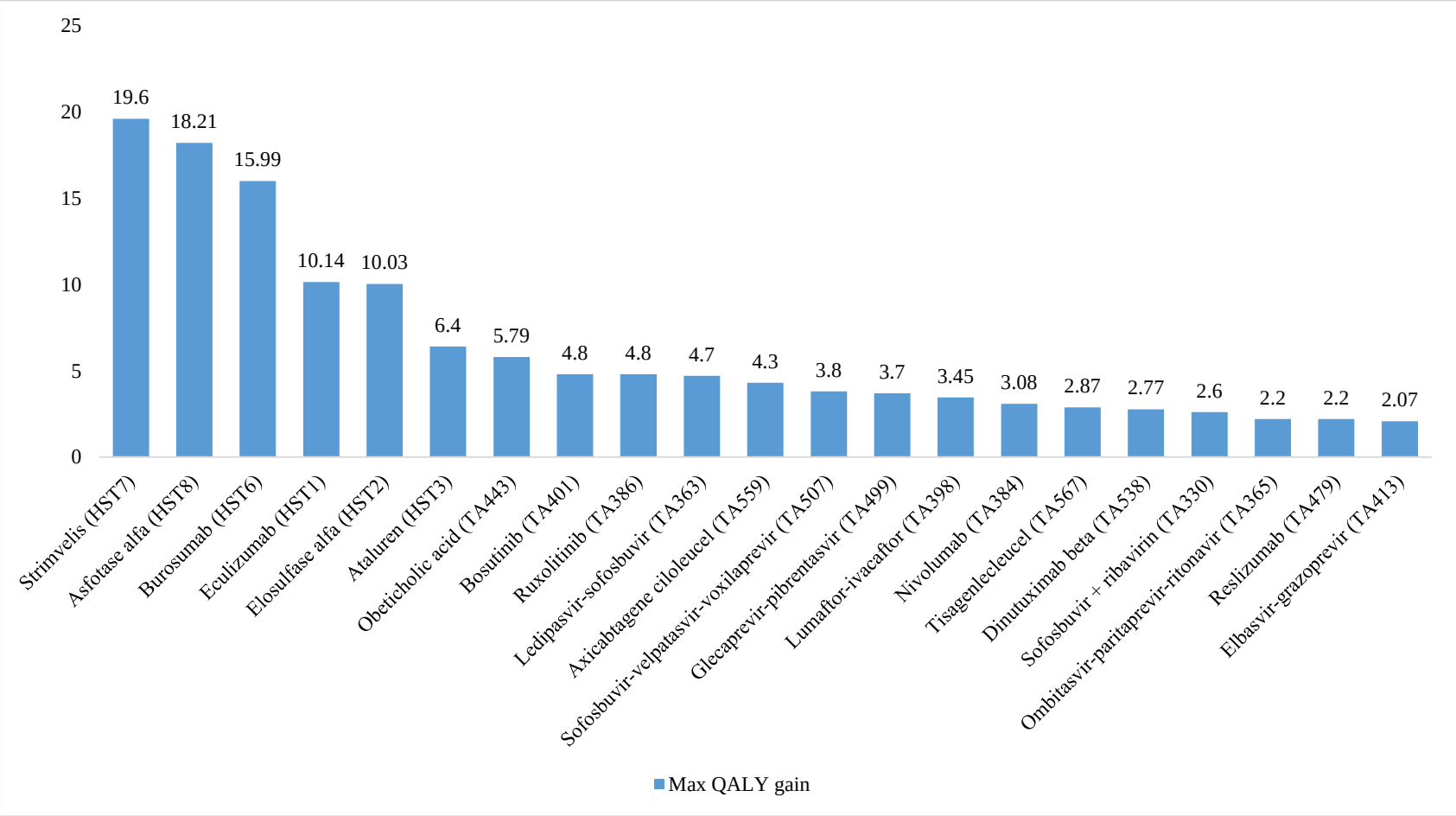
Intervention **NICE ID (Year of appraisal)**	**Condition**	**Intervention type** **Mechanism of action**	**QALY gain**
Ataluren HST3 (2016)	Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk	Drug (oral) Allows protein-making apparatus in cells to skip over the nonsense mutation, and cells to produce a full length functional dystrophin protein	2.4 to 6.4
Obeticholic acid TA443 (2017)	Primary biliary cholangitis in inadequate responders/ intolerant to ursodeoxycholic acid	Drug (oral) Farnesoid-X receptor agonist and modified bile acid	5.79
Reslizumab TA479 (2017)	Severe eosinophilic asthma in adults that is inadequately controlled with high-dose inhaled corticosteroids plus another drug, plus blood eosinophil count of ≥400 cells per microlitre and following 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months	Drug (intravenous) Monoclonal anti-interleukin-5 antibody	2.2
Asfotase alfa HST6 (2017)	Paediatric-onset hypophosphatasia	Drug (subcutaneous injection) Recombinant fusion protein to restore the regulation of metabolic processes in the bones and teeth	13.47 to 18.21
Glecaprevir-pibrentasvir TA499 (2018)	Chronic hepatitis C (all genotypes)	Drug (oral) HCV NS3 protease inhibitor and HCV NS5A inhibitor	2.3 to 3.7
Sofosbuvir-velpatasvir-voxilaprevir TA507 (2018)	Chronic hepatitis C (all genotypes)	Drug (oral) Pan-genotypic nucleotide analogues inhibiting non-structural protein 5B, NS5A and NS3/4A	3.4 to 3.8
Dinutuximab beta TA538 (2018)	High-risk neuroblastoma in people aged 12 months plus partial responders to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if not previously treated with anti-GD2 immunotherapy	Drug (intravenous) Chimeric monoclonal antibody targeting GD2, a glycolipid expressed in neuroblastoma tumours.	1.89 to 2.77
Tisagenlecleucel TA554 (2018)	Relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years	Gene therapy (intravenous) Chimeric antigen receptor (CAR) T cell therapy binding to CD-19 expressing cells	redacted
Tisagenlecleucel TA567 (2018)	Relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Gene therapy (intravenous) Chimeric antigen receptor (CAR) T cell therapy binding to CD-19 expressing cells	2.17 to 2.87

Intervention **NICE ID (Year of appraisal)**	**Condition**	**Intervention type** **Mechanism of action**	**QALY gain**
Axicabtagene ciloleucel TA559 (2018)	Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Gene therapy (intravenous) Immunotherapy using autologous T cells directed against the tumour antigen CD19	4.3
Burosumab HST8 (2018)	X-linked hypophosphataemia with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing bones	Drug (subcutaneous injection) Human monoclonal antibody which binds to FGF23 increasing production of 1,25-dihydroxyvitamin D	5.52 to 15.99
Strimvelis HST7 (2018)	Adenosine deaminase deficiency–severe combined immunodeficiency when no suitable human leukocyte antigen-matched related stem cell donor is available.	Gene therapy (intravenous) Containing autologous CD34+ cells, transduced ex vivo with a replication-deficient retroviral vector containing the correct form of the human ADA gene in the DNA sequence	14 to 19.6

3.1.1. Interventions ordered by QALY gain

Figure 1 shows the interventions from the appraisals identified, ordered by their maximum estimated QALY gain. Highly specialised technologies (HST) represent the six highest estimated QALY gains (HST7, HST6, HST8, HST1, HST2 and HST3). HST appraisals only consider new and emerging healthcare technologies for very rare conditions.

Figure 1. Interventions* under appraisal ordered by maximum estimated QALY gain

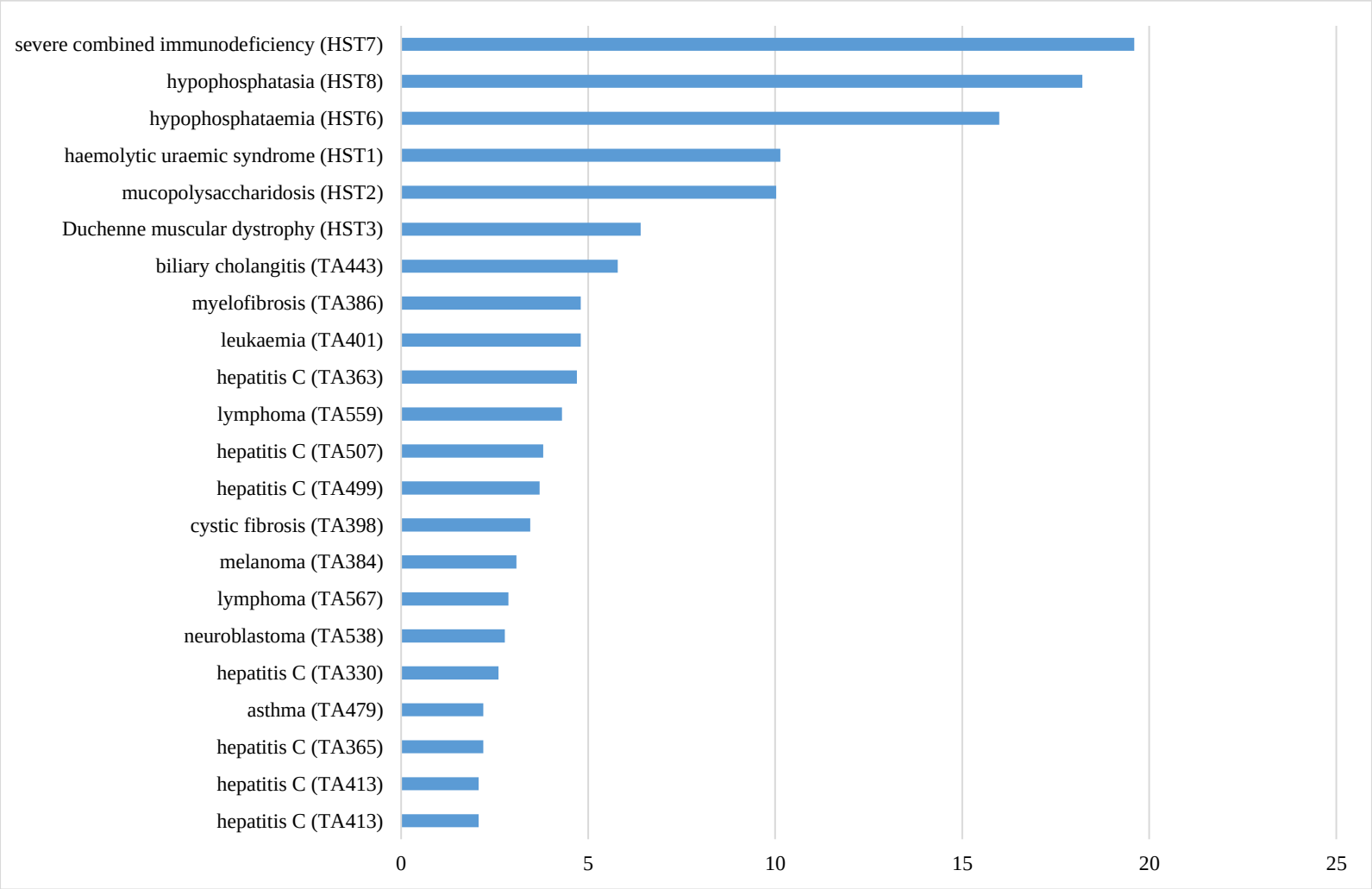


*Note: does not include Tisagenlecleucel for leukaemia (TA554) as the estimated QALY gain was redacted

3.1.2. Target conditions of the included technology appraisals

Figure 2 demonstrates the conditions treated by the technologies under appraisal, ranked by maximum estimated QALY gain.

Figure 2. Medical conditions* under appraisal ranked by maximum estimated QALY gain



*Note: does not include appraisal for leukaemia (TA554) as estimated QALY gain was redacted.

3.1.3. Target population and standard of care in included appraisals

Characteristics of the conditions of the included appraisals including the prevalence, life expectancy and comparator in standard of care are described in Table 2.

Table 2. Population characteristics and comparators in included appraisals

Intervention and target condition	Prevalence of target condition	Life expectancy	Comparator
Chronic hepatitis C			
Sofosbuvir for chronic hepatitis C	Around 160,000 in England	Unclear. Average age of death with liver disease 59 years. Mortality rates were three times higher than those expected in the general population. Cirrhosis develops after 20-30 years in 30% of hepatitis C virus cases	ribavirin and peginterferon alfa-2a/-2b
Ledipasvir-sofosbuvir for chronic hepatitis C			
Ombitasvir-paritaprevir-ritonavir (2D) for chronic hepatitis C			
Elbasvir-grazoprevir for chronic hepatitis C			
Glecaprevir-pibrentasvir for chronic hepatitis C			
Sofosbuvir-velpatasvir-voxilaprevir for chronic hepatitis C			
Chronic or inherited conditions			
Burosumab for X-linked hypophosphataemia in children and young people	250 children, 2500 adults in England with condition	No impact on life expectancy	SoC (phosphate/vitamin D supplementation)
Asfotase alfa for paediatric-onset hypophosphatasia	187 hospital admissions in England in 2011. 1 per 300,000 live births in Europe	Most patients die at birth or within first year of life	SoC (vitamin B6 supplementation)
Lumacaftor-ivacaftor plus SoC for cystic fibrosis homozygous for the F508del mutation	1 in 2500 live births have cystic fibrosis and 52% of these have F508del mutation	Average lifespan around 40 years	Best supportive care including mannitol dry powder, inhaled mucolytics, nebulised hypertonic

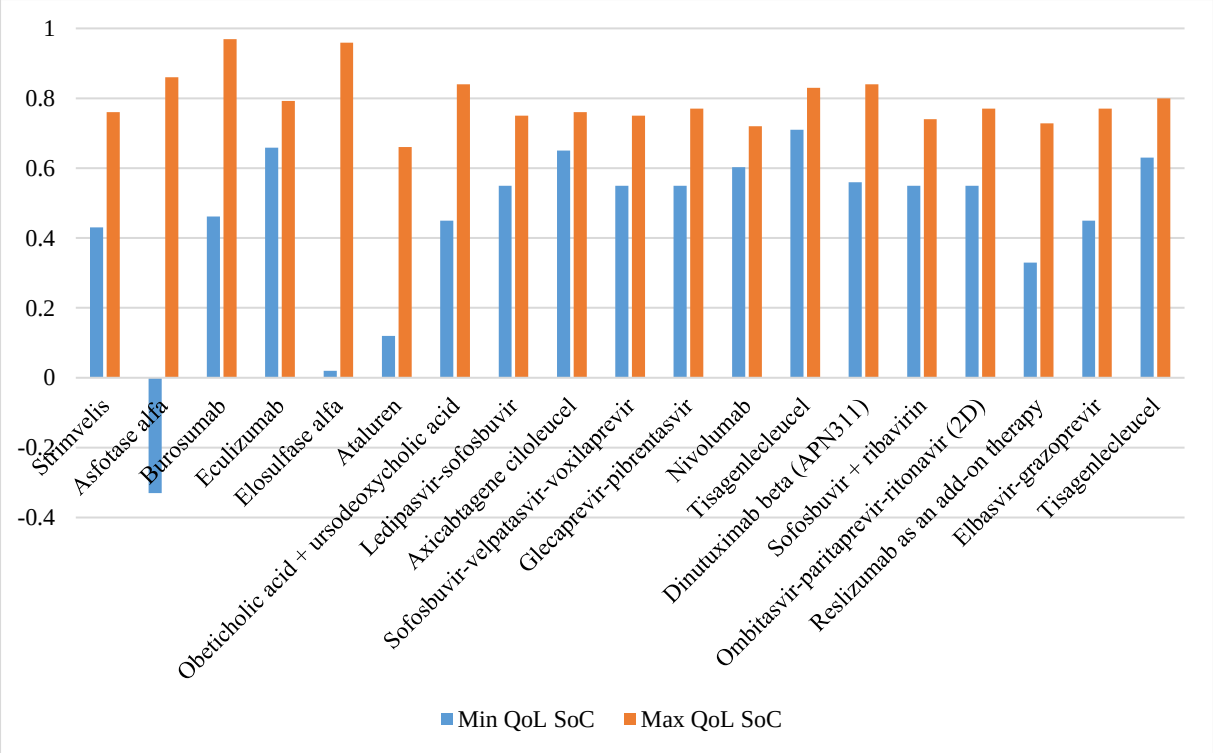
Intervention and target condition	Prevalence of target condition	Life expectancy	Comparator
			saline, anti-inflammatory agents, bronchodilators, pancreatic enzymes, and oral, nebulised and intravenous antibiotics
Ataluren for Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	13% of DMD (10 boys born each year in UK)	Average lifespan less than 30 years	Established clinical management without ataluren including corticosteroids, and management of cardiac, pulmonary, orthopaedic and gastrointestinal complications
Obeticholic acid + ursodeoxycholic acid for primary biliary cholangitis	35 people per 100,000 (18,900 in England)	Average time to death 22 years after first appearance of anti-mitochondrial antibodies	Ursodeoxycholic acid
Eculizumab for atypical haemolytic uraemic syndrome	140 people with a diagnosis of aHUS in England	5-year survival without end-stage renal failure was 64% in children and 36% in adults	plasma infusion/ dialysis/ kidney or liver transplant
Elosulfase alfa for mucopolysaccharidosis type IVa	1 person per 220,000 live births, equating to about 3 new diagnoses per year in England	Patients generally die in their second or third decade of life	Established clinical management (supportive or palliative) including surgery
Reslizumab as an add-on therapy for severe eosinophilic asthma	Around 5.4 million in England and Wales receive treatment for asthma	Unclear. Majority (>60%) of fatalities occur in those aged ≥65 years	inhaled beta-2 agonist, corticosteroids, omalizumab
Strimvelis for adenosine deaminase deficiency–severe combined immunodeficiency	10 people born per year in England; between 1 in 200,000 and 1 in 1,000,000 live births	Children rarely survive beyond 2 years Appraisal committee agreed end of life criteria met (life expectancy less than 24 months)	Bone marrow transplant
Cancer			
Bosutinib for previously treated chronic myeloid leukaemia	1.0 per 100,000 population	5-year relative survival: 89.1%	nilotinib or imatinib or dasitinib
Nivolumab for advanced (unresectable or metastatic) melanoma	11,281 new diagnoses and 1781 deaths in England in 2012	5–22% of stage IV will live longer than 5 years	ipilimumab or BRAF inhibitors
Ruxolitinib for myelofibrosis	0.75 per 100,000, 10-20% develop acute myeloid leukaemia	Median survival is 5 years from onset. Appraisal committee agreed half met EoL criteria (less than 24 months life expectancy)	SoC including hydroxycarbamide, other chemos etc.

Intervention and target condition	Prevalence of target condition	Life expectancy	Comparator
Dinutuximab beta for neuroblastoma following myeloablative therapy and autologous stem cell transplant	Usually affects children age 5 years. Around 90 diagnosed each year in UK.	Median 4 years from onset	multi-agent chemotherapy, surgery and radiotherapy
Tisagenlecleucel for relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years	Most common in children, adolescents and young adults. 654 diagnosed with ALL in 2014	Overall survival rate at 5 years is approximately 10%	chemotherapy combinations, blinatumumab, ponatinib, stem cell transplantation
Tisagenlecleucel for relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	11,690 new cases in 2015	5-years survival rate 65-70% for stage I and II and 50% at stages III and IV	rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
Axicabtagene ciloleucel for diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	11,690 new cases in England in 2015	5-years survival rate 65-70% for stage I and II and 50% at stages III and IV	rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

3.1.4. Quality of life for standard of care

In order to assess the quality of life for conditions under appraisal, data were sought on the utilities used in the company's economic model (values between 0 and 1). Data were extracted for nineteen appraisals where relevant data were not redacted due to confidentiality. These values indicate the average quality of life values used in the economic model for the worst and best health states at baseline or for the comparator/SoC, and are displayed in Figure 3. However, these data should be interpreted with caution as it was not possible to obtain consistent utility values between appraisals due to heterogeneity in the modelling approaches used, the modelling of multiple health states and the frequency of confidential marking for utilities data. Visual inspection of the nineteen appraisals for which data were available provides no obvious patterns other than some very low minimum quality of life values occurring across appraisals.

Figure 3. Minimum and maximum quality of life values for SoC, ordered by largest QALY gain



4. THEMATIC ANALYSIS

The appraisals identified as producing large QALY gains relate to technologies which are considered as producing substantial health benefits. However, these technologies are not necessarily deemed to be cost-effective using the standard NICE thresholds (between £20,000-30,000). Nor does it necessarily follow that technologies which estimate large QALY gains consistently receive a positive NICE recommendation. For example, lumacaftor-ivacaftor plus SoC (TA398) is not currently recommended by NICE despite estimated QALY gains of 3.45. Additionally many technologies are recommended only if provided:

- with a patient access scheme (TA401, TA365, TA386, HST3, TA443, TA479)
- in line with the managed access agreement (HST2, HST6, TA507, TA567)
- at the same price or lower than that agreed with the Commercial Medicines Unit (TA413, TA499)
- through commercial arrangement (TA538, HST8)
- through the Cancer Drugs Fund (TA554, TA559).

These additional requirements for a positive recommendation from NICE indicate that there are conditions that inform the evaluation of the technology's potential value and place in the NHS that extend beyond the estimated QALY gain. NICE considers recommending the use of technologies in the NHS on the basis of innovation and promoting health equity.

It is therefore important to consider what the corresponding NICE appraisal committee considered be the valid potential benefits and wider impact of the intervention on patients, the clinical care pathway, the health service and wider societal impact.

This section therefore presents themes:

i. identified from common characteristics of appraisals
ii. identified from company therapeutic value propositions and committee discussion on innovation of the new technology.

4.1. THEMES FROM COMMON CHARACTERISTICS OF APPRAISALS

Four themes were identified from data extraction of the common characteristics of the included technology appraisals in terms of the conditions being treated.

4.1.1. Chronic conditions

Over half of appraisals (14/22) are in chronic conditions including six in hepatitis C, and one each in: hypophosphatasia, hypophosphataemia, cystic fibrosis, Duchenne muscular dystrophy, primary biliary cholangitis, atypical haemolytic uraemic syndrome, mucopolysaccharidosis type Iva, and asthma.

Nature and symptoms of the chronic conditions appraised:

Chronic hepatitis C (TA330, TA363, TA365, TA413, TA499, TA507) is an infectious disease which leads to liver damage and is associated with reduced health related quality of life (HRQoL) including fatigue, psychological issues including depression and anxiety and impairment on activities of daily living. The technologies were indicated for both treatment experienced and treatment-naïve patients in patients with and without liver cirrhosis.

Paediatric-onset hypophosphatasia (HST6) is a rare, inherited disorder which disrupts mineralisation, causing bone deformity and a greater incidence of fractures. Symptoms include poor feeding and respiratory problems in infancy, short stature, weak and soft bones; short limbs; other skeletal abnormalities and hypercalcemia. Complications can be life-threatening. Most patients with perinatal-onset disease die at birth or within first year of life. The technology (asfotase alfa) was indicated for paediatric-onset hypophosphatasia. Prior to this there were no treatments for hypophosphatasia and clinical management aimed to monitor and alleviate symptoms.

X-linked hypophosphataemia (HST8) is a genetic bone disease starting in early life which varies in severity. Symptoms include rickets and skeletal deformities causing daily pain, muscle weakness and fatigue. Impairments to HRQoL include physical and psychosocial functioning but the condition is not thought to impact life expectancy. Prior to the technology (burosumab) there were no treatments that targeted the underlying cause. Medical management was aimed at improving growth, decreasing morbidity, and preventing skeletal deformities. XLH does not respond to vitamin D supplementation alone. Burosumab was indicated for people with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing bones.

Cystic fibrosis (TA398) is a life-limiting and debilitating disease featuring pulmonary exacerbations and poor nutritional status with poor disease control, which are highly associated with mortality. Mental health problems, including anxiety and depression are frequently reported in both patients and caregivers. The technology (lumacaftor–ivacaftor) was indicated for patients with the F508del mutation aged 12 years and over.

Duchenne muscular dystrophy (HST3) is a rare, severe, life-limiting and inherited condition. Males are affected from the age of three years and disease-related mortality occurs generally during the third decade of life. It is a degenerative neuromuscular condition involving gait loss, pain and functional dependence on carers causing impact upon daily activities for patients and their families. The technology (ataluren) was indicated for patients in the early stages of the disease (aged 5 years and older who are able to walk).

Primary biliary cholangitis (TA443) is a progressive autoimmune disease mostly prevalent in women which leads to liver failure. Physical and mental HRQoL are stated to be lower than the general population. Up to half of people do not have symptoms until extensive liver damage occurs. Liver failure is the usual cause of death in most patients. The technology (obeticholc acid) was indicated for those whose disease has an inadequate response to, or who are unable to tolerate the active comparator, ursodeoxycholic acid.

Atypical haemolytic uraemic syndrome (HST1) is a rare, progressive, life-threatening disease causing blood clots in the kidneys. Poor disease control can lead to end-stage renal failure and shortened life span. Symptoms extend across the central nervous system, gastrointestinal, cardiac and pulmonary systems. Dialysis and other supportive care measures required impact daily living. The technology (eculizumab) was indicated as first-line treatment from patients at first presentation through to those listed for renal transplant.

Mucopolysaccharidosis type Iva (HST2) is a rare, multi-systemic progressive disease across respiratory, cardiac and musculoskeletal faculties causing death generally before 40 years of age. Symptoms include short stature, progressive loss of endurance leading increased wheelchair use, fatigue, pain and functional capacity which impacts HRQoL and daily living. The technology (elosulfase alfa) was indicated for all patients with the condition.

Severe eosinophilic asthma (TA479) involves elevated eosinophil levels resulting in exacerbations and acute respiratory events, which can lead to hospitalisation or death. Treatment involves high doses of corticosteroids which can result in substantial side effects. HRQoL can be impaired with poor disease control. Asthma can be a life-threatening condition but is not considered to impact life expectancy. The technology (reslizumab) was indicated as an add-on therapy for asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug.

Adenosine deaminase deficiency (HST7) or severe combined immunodeficiency is an inherited disorder. People with severe combined immunodeficiency are prone to persistent infections that can be serious or life-threatening. The main symptoms are pneumonia, chronic diarrhoea, and widespread skin rashes. Affected children also grow much more slowly than healthy children and may have developmental delay. Most individuals with ADA deficiency are diagnosed with SCID in the first 6 months of life do not survive past age two without treatment. The technology (strimvelis) was recommended when no suitable human leukocyte antigen-matched related stem cell donor is available.

4.1.2. Cancer

Seven appraisals were of treatments for cancer including leukaemia (TA401 & TA554), melanoma (TA384), myelofibrosis (TA386), neuroblastoma (TA538), lymphoma (TA567 & TA559). The technologies tended to be indicated or recommended as later lines of treatment for advanced, relapsed or refractory cancer patients (see Table 3).

Table 3. Cancer stages by drug indication and NICE recommendation

Cancer (appraisal)	**Indication**	**NICE Recommendation**
leukaemia (TA401)	'chronic', 'accelerated' and 'blast' phases of CML in patients that have already been treated with one or more tyrosine kinase inhibitors or when dasatinib, imatinib and nilotinib are not suitable	previously had 1 or more tyrosine kinase inhibitor and imatinib, nilotinib and dasatinib are not appropriate
leukaemia (TA554)	relapsed or refractory B-cell acute lymphoblastic	relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years
melanoma (TA384)	unresectable or metastatic	advanced (unresectable or metastatic)

myelofibrosis (TA386)	primary, intermediate and high-risk	primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis in people with intermediate-2 or high-risk disease
neuroblastoma (TA538)	following myeloablative therapy and autologous stem cell transplant	high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if they have not already had anti-GD2 immunotherapy
lymphoma (TA567)	relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma or transformed follicular lymphoma	relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies
lymphoma (TA559)	relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma	relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies

4.1.3. Low life expectancy

The two appraisals producing the largest QALY gains were treatments for infants expected to die between birth and two years of age (HST7 & HST6). Strimvelis (HST7) for adenosine deaminase deficiency–severe combined immunodeficiency also featured a 100% response rate indicating a clear link to the large estimated QALY gains. HST6 for Asfotase alfa is a disease-modifying drug in paediatric-onset hypophosphatasia; a condition for which there was no treatment indicating the substantial unmet clinical need underpinning the large QALY gains.

Eight appraisals were of patient conditions with median overall survival less than 5 years (HST1, TA384, TA386, HST6, TA538, TA554, TA567, TA559). The appraisal of ruxolitinib (TA386) concluded that half of eligible patients with myelofibrosis met end of life criteria.

Some appraisals however noted that the conditions exhibited no clear impact on overall life expectancy such as asthma (TA479) and hypophosphataemia (HST8).

4.1.4. Children

The two appraisals producing the largest QALY gains are conditions affecting infants (HST7 & HST6). Large QALY gains are likely to be attributed to technologies that provide potential

lifetime benefit. Other appraisals in children and adolescents include HST2, HST3, TA538 and TA554.

4.2. THEMES FROM COMPANY THERAPEUTIC VALUE PROPOSITIONS AND NICE COMMITTEE DISCUSSION

Company submissions to NICE present information about the potential novelty of the technology and its position in the current clinical pathway. These TVPs discuss how innovative the technology is and whether it will lead to a step-change in patient care. TVPs may or may not be supported by evidence therefore the NICE appraisal process features committee discussion about what elements of the technology they agree are innovative or result in a step-change. A summary of this discussion is normally presented in the FAD. Neither company submission nor FADs can be considered as comprehensive sources of information as TVPs proposed by the company may remain unsubstantiated and FADs may not reflect the entirety of the committee discussion. Themes from either source were extracted, coded and categorised into potentially relevant conceptual domains.

Twenty-five themes were identified from TVPs in company submissions and committee discussion in FADs, which were subsequently categorised into four underpinning conceptual domains.

4.2.1. Themes regarding the innovation of the technology that may lead to substantial health-related benefits

Eight themes identified across appraisals related to the innovation of the technology leading to substantial health-related benefits or a step-change in patient care. These are:

i. Cure (n=8: TA363, TA365, TA384, TA507, TA554, TA567, TA559, HST7)

ii. Provides treatment where standard care only offered symptom management (n=12: HST1, HST2, TA386, TA398, HST3, TA443, TA479, HST6, TA554, TA567, TA559, HST7)

iii. Provides a novel mode of administration e.g. oral as opposed to intravenous (n=5: TA363, TA365, TA398, TA499, TA538)

iv. Addresses unmet need in specific biological subgroups e.g. genotype or mutation (n=4: TA330, TA365, TA386, TA413)

v. Produces substantial, or prolonged, clinical benefit (n=16: TA363, TA365, HST2, TA384, TA386, HST3, TA443, TA479, HST6, TA507, TA538, TA554, TA567, TA559, HST8, HST7)

vi. Addresses unmet need in "difficult to treat" patients or those ineligible for the active comparator (n=16: TA401, TA330, TA363, HST2, TA384, TA386, TA413, HST3, TA443, TA479, TA499, TA507, TA554, TA567, TA559, HST7)

vii. Negates the toxicity or risks of the comparator treatment (n=16: TA401, TA330, TA363, TA365, HST1, TA384, TA386, TA398, TA413, TA443, TA479, TA499, TA538, TA559, HST8, HST7)

viii. Mechanism of action targets underlying cause of disease (n=9: HST2, TA386, HST3, HST6, TA554, TA567, TA559, HST8, HST7)

4.2.2. Themes regarding substantial benefits to clinical management of disease or the health service

Eight themes identified across appraisals related to substantial benefits to clinical management of disease or the wider health service. These are:

i. Enables treatment in outpatient setting (n=1: TA538)

ii. Improves patient adherence/compliance (n=4: TA384, TA479, TA538, TA559)

iii. Avoids treating side effects of comparator treatments (n=5: TA363, TA365, TA398, TA479, TA538)

iv. Simplified treatment /reduces clinical staff time (n=10: TA363, TA365, HST1, TA398, TA413, TA499, TA554, TA559, HST8, HST7)

v. Reduces hospitalisations (n=3: TA398, TA479, TA507)

vi. Negates need for biological pre-treatment screening (n=3: TA499, TA507, HST7)

vii. Avoids need for later surgery or transplant (n=2: TA443, HST8)

viii. Avoids need for complex treatment of a chronic disease e.g. dialysis, stem cell transplant (n=3: TA386, HST8, HST7)

4.2.3. Themes regarding benefits that may not be part of the Incremental Cost-Effectiveness Ratio (ICER) calculation

Seven themes identified across appraisals related to benefits discussed by the company or the NICE appraisal committee that may not be part of the ICER calculation. These are:

i. Facilitates economic productivity or patients improved earning capacity (n=4: TA363, TA365, TA398, TA554)

ii. Alleviates carer burden/ addresses wider family QoL (n=4: TA398, TA479, TA554, HST7, HST8)

iii. Likely to stimulate research/ opens way to new treatments (n=3: HST2, TA384, TA443)

iv. Reduces disease transmission (n=5: TA330, TA363, TA365, TA413, TA507)

v. Reduces health inequalities (n=5: TA365, HST1, TA386, TA499, TA507)

vi. Provides psychological benefits (n=1: TA363)

vii. Advances understanding of disease (n=1: HST2)

4.2.4. "Wildcard" themes noted by the NICE committee in the FAD

Two themes identified across appraisals related to notable mention by the NICE appraisal committee during the FAD. These are:

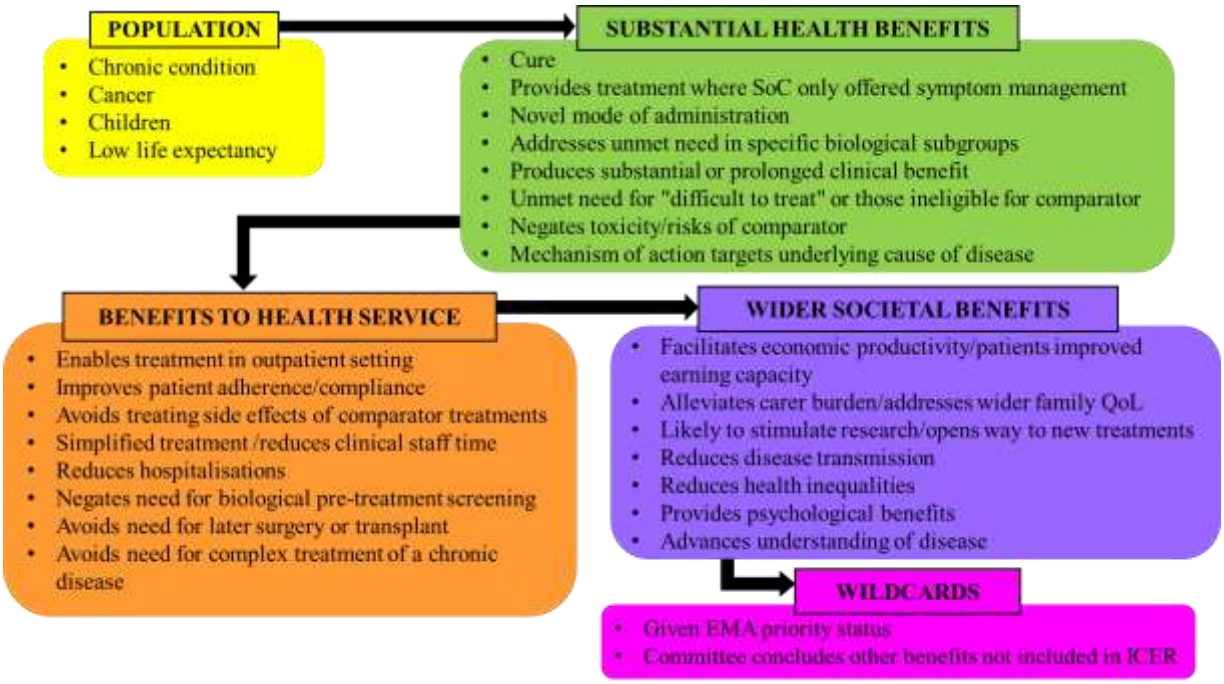
i. Given PRIME priority status through the European Medicines Agency to enhance support for the development of medicines that target an unmet medical need (n=3: TA554, TA567, TA559)

ii. Likely to provide benefits not included in the ICER (n=10: TA330, TA363, TA365, HST1, TA398, TA413, TA443, TA554, HST8, HST7)

5. FRAMEWORK OF THEMES

An illustration of the framework of themes identified by the thematic analysis is shown in Figure 4. Generally, the underpinning conceptual domains are arranged in the order they are potentially likely to directly drive QALY gains. It is not possible to state which themes definitely drive the QALY gain without quantitative analysis of all (unredacted) appraisals. Whilst not all themes identified may be directly related to a large QALY gain, the themes identify common characteristics of the appraisal, the technology, the patient population, the clinical pathway or the wider decision problem that contributed to the technology's therapeutic value proposition and ultimately the NICE recommendation.

Figure 4. Framework of themes identified from appraisals with large estimated QALY gains



5.1. FREQUENCY OF THEMES ACROSS APPRAISALS

The frequency of themes related to the population, innovation of the technology producing substantial health-related benefits, benefits to clinical management of patients or health service and wider societal benefits and wildcards from committee discussion, across all appraisals, is presented in Figure 5.

Figure 5. Frequency of themes mapped by NICE appraisal (ordered chronologically)

THEME \ NICE ID	TA401	TA330	TA363	TA365	HST1	HST2	TA384	TA386	TA398	TA413	HST3	TA443	TA479	HST6	TA499	TA507	TA538	TA554	TA567	TA559	HST8	HST7
Chronic conditions		✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓						
Cancer	✓						✓	✓									✓	✓	✓	✓		
Low life expectancy					✓		✓	✓						✓			✓	✓	✓	✓		✓
Children						✓		✓			✓			✓			✓	✓				
Cure			✓	✓			✓									✓		✓	✓	✓		✓
Provides treatment where SoC only offered symptom management					✓	✓		✓	✓		✓	✓	✓	✓				✓	✓	✓		✓
Novel mode of administration			✓	✓					✓						✓		✓					
Addresses unmet need in specific biological subgroups		✓		✓				✓		✓												
Produces substantial or prolonged clinical benefit			✓	✓		✓	✓	✓			✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Unmet need for "difficult to treat" or those ineligible for comparator	✓	✓	✓			✓	✓	✓		✓	✓	✓	✓		✓	✓		✓	✓	✓		✓
Negates toxicity/risks of comparator	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓		✓		✓			✓	✓	✓
Mechanism of action targets underlying cause of disease						✓		✓			✓			✓				✓	✓	✓	✓	✓
Enables treatment in outpatient setting																	✓					
Improves patient adherence/compliance							✓						✓				✓			✓		
Avoids treating side effects of comparator treatments			✓	✓					✓				✓				✓					
Simplified treatment /reduces clinical staff time			✓	✓	✓				✓	✓					✓			✓		✓	✓	✓
Reduces hospitalisations									✓				✓			✓						
Negates need for biological pre-treatment screening															✓	✓						✓
Avoids need for later surgery or transplant												✓									✓	
Avoids need for complex treatment of a chronic disease								✓													✓	✓
Facilitates economic productivity/patients improved earning capacity			✓	✓					✓									✓				
Alleviates carer burden/addresses wider family QoL									✓				✓					✓			✓	✓
Likely to stimulate research/opens way to new treatments						✓	✓					✓										
Reduces disease transmission		✓	✓	✓						✓						✓						
Reduces health inequalities				✓	✓			✓							✓	✓						
Provides psychological benefits			✓																			
Advances understanding of disease						✓																
Given EMA priority status																		✓	✓	✓		
Committee concludes other benefits not included in ICER		✓	✓	✓	✓				✓	✓		✓						✓			✓	✓

Figure 6. Frequency of themes

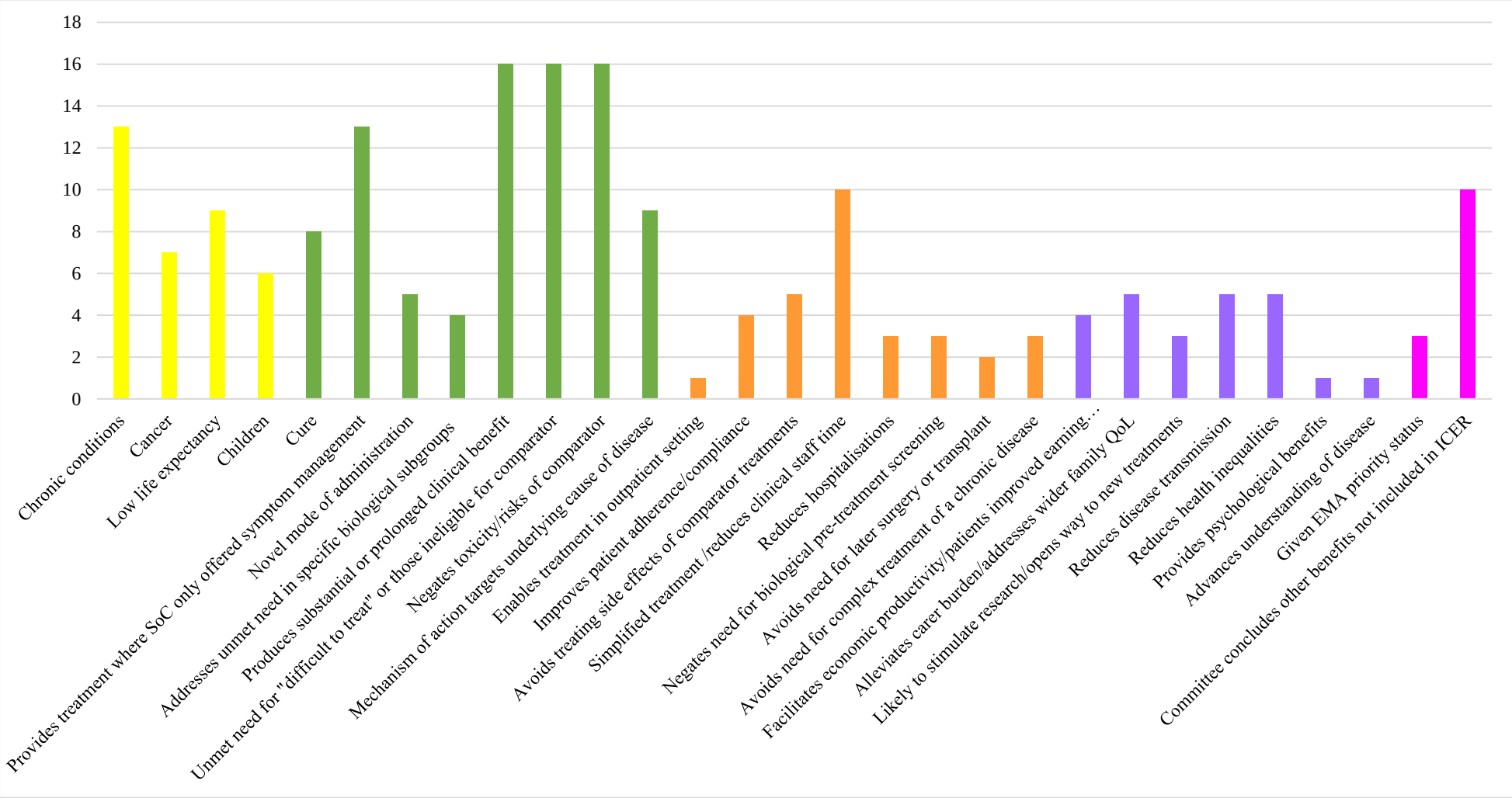


Figure 7. Frequency of themes presented numerically

6. DISCUSSION AND CONCLUSIONS

A range of common features were identified among technologies that have previously demonstrated two QALY gains that can be used to identify early stage technologies with the potential to deliver major improvements in health outcomes. The results should be interpreted with caution due to the reliance on retrospective analysis of completed appraisals and their subsequent ability to inform on potential prospective benefits of emerging technologies.

Twenty-nine unique themes were identified from the 22 NICE appraisals retrieved that were estimated to produce large QALY gains. Themes could broadly be categorised under five conceptual domains relating to (i) the population, (ii) the health benefits or step change from the intervention, (iii) the benefits to the health service that the intervention is likely to lead to, (iv) the wider benefits to society and (v) "wildcard" items noted from NICE committee discussion. Themes relating to the (i) population or medical condition under assessment were most likely to indicate a clear link to the large QALY gain (e.g., low life expectancy, children). The most frequently observed themes were related to (ii) the substantial health benefits of the technology. However, these claims are frequently proposed by the company at the time of submission to NICE and may not have been deemed to be valid or sustained by the appraisal committee. The conceptual framework of themes can inform guidance to highlight characteristics of early stage technologies with the potential to deliver major health improvements in health outcomes. However, therapeutic value propositions and consideration of innovation would need to be proposed by companies and reviewed by NICE early in the appraisal process. Evidence regarding the benefits of early stage technologies are likely to be reliant on early studies, which tend to exaggerate benefits, which then decline as longer-term evidence accumulates (Naci & Mossialos, 2017) [1].

A variety of therapeutic interventions were reviewed including oral drugs, subcutaneous and intravenous infusions to ex vivo gene therapy. The medical technologies evaluation programme and the NICE technology appraisal programmes do not completely align as the former focuses on approving technologies that are cost saving or cost neutral (NICE, 2011) [2] . Conversely diagnostic guidance is usually cost incurring at the outset with potential cost-saving benefits of new diagnostic interventions accrued later down the line. As no diagnostic or medical device appraisals were retrieved, the framework of themes cannot be assumed to be generalizable to

all NICE technology appraisal processes. Moreover, as large health gains are less likely to be observed during diagnostic appraisals this limits the applicability of the themes identified in this review to diagnostic appraisals.

The NICE technology appraisal process aims to consider cost-effectiveness where health benefits are greater than the opportunity costs of programmes displaced to fund the new technology, in the context of a fixed NHS budget (NICE, 2013) [3]. Within these criteria, technologies of an innovative nature can be considered for funding by the NHS even when they do not satisfy NICE's cost-effectiveness criteria, if they are deemed likely produce large health gains with a favourable risk-benefit balance at an acceptable cost. The effort to promote healthcare innovation by NICE is considered (Charlton & Rid, 2019) [4] under three criteria:

1) Novelty: the technology under consideration has innovative characteristics
2) Substantial benefits: these characteristics lead to substantial health-related benefits
3) Demonstrable and uncounted benefits: requires that the benefits be supported by adequate evidence and not already be part of the standard ICER calculation, thereby preventing double counting.

Despite this margin for special consideration of innovation by NICE, companies, ERGs and appraisal committees are likely to vary in the attention heeded to the consideration of innovation. The rapid timeframe of this thematic analysis required reliance on overview, summary and discussion documents. Therefore it is not clear what aspects of a technology's innovative nature have been consistently invoked by NICE in order to justify recommending technologies which are insufficiently cost-effective.

6.1. LIMITATIONS OF THE THEMATIC ANALYSIS

Limitations of the work undertaken to be considered in interpretation include:

- Searches for relevant technology appraisals were not systematic or exhaustive. Relevant appraisals were identified via a cursory analysis that has not been independently checked by a second reviewer.
- Descriptive characteristics were not consistently comparable between appraisals due to different populations, conditions, company descriptions, redacted information etc.

- Due to re-iterations of company responses to the NICE appraisal process, some appraisals involved several committee meetings and associated papers, therefore information used to extract data was not consistently reliably at every iteration.
- Therapeutic value propositions proposed by the companies include claims from manufacturers about the technology or decision problem that may not be substantiated by evidence.
- FADs are unlikely to reflect committee deliberation in its entirety so it is possible that committees gave more or less weight to a technology's innovative nature than the published documents assessed convey.
- The cut-off of two QALYs is arbitrary and there is no assessment of whether the themes identified are also prevalent in those that generate less than 2 QALYs of health gain.

6.2. CONCLUSIONS

Due to the wide range of themes identified across fairly heterogeneous medical conditions, it is not possible to *concisely* describe the characteristics of an early stage technology with the potential to deliver major improvements in health outcomes. However, some commonality across appraisals on a wide variety of themes indicate a promising starting point to ensure that the available information for early stage technologies is assessed comprehensively in order for the potential opportunities for technologies capable of producing large QALY gains to be considered. Some aspects of the potential value of new technologies will not be known for products at an early stage of development (e.g. significant clinical benefit) therefore companies and the AAC will need to be (cautiously) proactive in establishing which aspects of the emerging decision problem align with the themes from these previous appraisals that estimated large QALY gains. Future research should aim to confirm whether the themes identified are also prevalent in appraisals which do not produce large QALY health gains. Additionally the themes could be prospectively validated to examine whether they are present (or indeed, whether further themes are present) in future appraisals which produce large estimated QALY gains.

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3. National Institute for Health Clinical Excellence, *Guide to the methods of technology appraisal 2013.* NICE, 2013.
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APPENDICES

A.1 DATA EXTRACTION SCREENSHOT FOR COMPANY TVPS

Intervention	NICE ID	Company Therapeutic Value Proposition	Code company themes
Bosutinib	TA401	Bosutinib treatment is innovative in so far as it has been proven to be clinically effective for a sub group of the CML patient population who are either resistant to or are unable to tolerate all other licensed TKIs. It is not innovative in the sense that it represents a step change in approaches to the treatment of CML. Approximately 75- 80% of patients respond satisfactorily to Imatinib / Nilotinib and achieve complete cytogenetic responses, but the remaining 25% of patients either cannot tolerate the drugs due to side effects and toxicity, or are refractory to these drugs and fail to achieve adequate responses. One cause of a failure to respond is the acquisition of bcr-abl mutations which prevent the binding of, or block the action of the tyrosine kinase inhibitor	A6 A7
Sofosbuvir + ribavirin	TA330	unmet need for cost-effective treatment option for genotype (GT) 1 and GT 4 treatment experienced patients. offers the possibility of shortened interferon-based treatment regimens thereby reducing potential adverse effects with interferon-based therapy, or treatment without interferon therapy in some circumstances, which is particularly important and a major development in the current clinical management of chronic hepatitis C. address an unmet need, particularly in people who have previously been treated but did not have a sustained virological response, in people whose condition has relapsed, or in people who have become re-infected after treatment.	A4 A7 A6
Ledipasvir-sofosbuvir	TA363	offers a step-change in efficacy, safety, and tolerability for the treatment of patients with HCV making successful HCV cure a realistic probability for an even higher proportion of patients, including those who currently have no or limited treatment options. very high cure rates in patients with HCV GT1, with additional data to support high cure rates in GT3 and GT4 infection.By eliminating interferon from the regimen and being formulated as a single tablet, LDV/SOF simplifies treatment into an all-oral, once daily IFN- and PI-free therapy. LDV/SOF is a highly efficacious treatment option, even for those who are ineligible or intolerant to IFN and thus currently have limited or no treatment options. ,Shorter treatment duration of 8 to 12 weeks (for the majority of GT1 and GT4 patients) compared with 24 to 48 weeks for established treatment options (PEG-IFN, TVR or BOC based regimens), 12 to 24 weeks for SOF-based regimens or 12 to 48 weeks for SMV-based regimens. LDV/SOF provides a favourable safety profile with only fatigue and headache identified as more common in patients treated with LDV/SOF than patients given placebo. The lack of significant drug interactions with immunosuppressant drugs and multiple antiretroviral regimens means that LDV/SOF can be used safely in liver transplant patients and patients with decompensated cirrhosis (including CPT B and C) or co-infected with HIV. These populations represent groups for which current treatment options are very limited and who are in urgent need of treatment.	A5 A1 A6 A3 A7 B4
Ombitasvir-paritaprevir-ritonavir (2D)	TA365	The 3D regimen for genotype 1 patients and the 2D regimen for genotype 4 patients should be considered a step change in the treatment of hepatitis C compared to current standard of care. These interferon-free regimens have the benefits of being all oral therapies with a dramatically improved tolerability and efficacy profile and significantly shorter treatment durations versus existing interferon containing regimens. Chance for viral cure. prevalent HCV in haemophila patients treated between 1970-1991. In addressing the appraisal NICE should be aware that HCV adversely affects certain populations who could be considered at risk of being disadvantaged in terms of accessing the healthcare system and therefore at risk of inequity of access to innovative new treatments. For example: - Certain immigrant populations - Prison population - Intravenous drug users.	A4 A7 A5 B4 A1 C6
Eculizumab	HST1	will maintain and enhance the international reputation that the UK has in the field of aHUS. will have an impact on the development of disease-specific working groups, care pathways, and the UK Registry for Rare Kidney Diseases (RaDaR). With NHS Kidney Care, care pathways are also being developed for aHUS which will become an integral part of the service. Alexion is also sponsoring an international aHUS registry that will capture and continue to follow aHUS patients irrespective of treatment status. . Eculizumab is simple to administer via intravenous (IV) infusion and is generally well-tolerated.	C3 B4
Elosulfase alfa	HST2	approved for the treatment of MPS-IVA; It is approved for use in MPS IVA patients of all ages; first treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, progressive and life-limiting disease. is an ERT; the goal of ERT in MPS IVA is to replace the deficient GALNS, reduce the accumulation of GAGs at cellular level and ultimately restore cellular function. first treatment option to have a positive impact on	A2 A8 A5
Nivolumab	TA384	step-change in treatment landscape through immunotherapy as potential cure?: 45-50% of patients estimated to be in remission 2 years after treatment initiation.	A1 A5
Ruxolitinib	TA386	significant umet treatment need in patients with intermediate-2 MF. currently no effective therapies approved for MF; conventional treatments provide limited or transient benefits and are associated with severe adverse events.66 The only existing therapy with curative potential is allogeneic stem cell transplantation (allo-SCT), but patient eligibility has been found to be as low as 1.5%, and mortality as high as 30%.67-69 There is therefore a significant unmet need for a therapy that: acts by targeting the underlying cause of the disease; can improve symptoms and HRQoL in patients with MF; is well tolerated; and is	A6 A2 A7 B9
ivacaftor plus SoC	TA398	No treatment options for F508del, only symptom management. Potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation	A2 B3
Elbasvir-grazoprevir	TA413	more favourable toxicity profile and useful for patient groups considered difficult to treat (prior treatment failures), those who are co-infected with HIV and HCV, and in those who are considered to have high unmet clinical need (CKD, stage 4-5). Effective and safe in patients receiving OST, thought to represent a significant number of patients in the UK primarily for those with chronic hepatitis C genotypes 1 and 4	A6 A7 A4
Ataluren	HST3	step-change: no other/previous disease modifying licensed therapies o treat underlying cause (loss of dystrophin). the only management options for this devastating disease were supportive in nature. Without dystrophin, muscles progressively weaken and deteriorate, leading to complete loss of ambulation, cardiac and respiratory insufficiency, and death. ataluren to change the course of disease independent of severity. high unmet medical need	A8 A2 A5 A6
Obeticholic acid + ursodeoxycholic acid	TA443	step-change. novel, innovative mechanism of action for patients with PBC, and is the first drug to be developed for patients with PBC in nearly 20 years. in those patients with PBC who have an incomplete response to UDCA, and where ALP is already significantly elevated, to prevent disease progression. unmet needs in PBC, with no treatment options for patients who have an inadequate response to, or are intolerant to, UDCA. These patients are at increased risk of complications, the requirement of a liver transplant, HCC, and death. Inadequate response to comparator in 70% of people- no other treatment option other than liver transplant	A2 A6 A7 B8
Reslizumab as an add-on therapy	TA479	No treatments are currently recommended by NICE for treating patients with eosinophilic (IL-5-mediated) asthma.few treatment options other than increasing doses; side effects of prolonged use of high dose inhaled or systematic corticosteroids; omalizumab is unsuitable for patients with severe eosinophilic asthma over half (53.4%) of patients at BTS/SIGN Step 4 or 5 have elevated eosinophil levels and would therefore be eligible for reslizumab therapy. Elevated eosinophils are associated with an increased frequency of asthma exacerbations and poor disease control (see Section 3.2.1). Asthma exacerbations are a prominent feature of poorly-controlled, severe asthma	A2 A7 B2 A6 B5
Asfotase alfa	HST6	currently no treatment for hypophosphatasia. first disease modifying drug that directly addresses the fundamental biochemical abnormality leading to hypophosphatasia and therefore fulfils an unmet clinical need. The company considered that the available evidence supports that asfotase alfa has a major impact on reducing disease morbidity and reducing the risk of mortality in people with paediatric-onset hypophosphatasia.	A2 A8 A5
Glecaprevir-pibrentasvir	TA499	simplify the clinical pathway of care in HCV by providing a well-tolerated, once-daily, oral treatment with a short (8 week) treatment duration in a large proportion of patients with HCV (i.e. TN NC patients), an anticipated pan-genotypic marketing authorisation, no requirement for baseline resistance-associated variant (RAV) and viral load testing in patient groups within the anticipated licence, and the potential to remove the requirement for genotyping to make treatment decisions. unmet need for patients with severe renal impairment and specific TE GT3 patients. cost of HCV treatment has a relatively high budget impact	B4 A3 B7 C6 A6
Sofosbuvir-velpatasvir-voxilaprevir	TA507	the only pan-genotypic STR available for the treatment of DAA-experienced patients, regardless of cirrhosis status. Clinical trial evidence indicates that SOF/VEL/VOX can offer high cure rates among this difficult to treat group. offers the realistic prospect of CHC cure to the small number of patients who do not achieve SVR after initial treatment with a DAA-containing regimen (including NS5A-containing regimens). There is currently no licensed and reimbursed pharmacologic treatment option for the retreatment of DAA-experienced patients, and limited guidance available to inform retreatment decisions. By not	B7 A1 A6 B5
Dinutuximab beta (APN311)	TA538	continuous infusion scheme, which shows major improvements of the safety profile by reducing pain and associated i.v. morphine use. possibility of receiving the treatment in outpatient setting, will facilitate patients remaining on therapy and receiving the full cycle of treatment, optimizing the possibility of long-term benefits. the Applicant has also demonstrated that co-administration of IL-2 is not superior compared to administration of the antibody alone in terms of efficacy, thus dinutuximab beta without this cytokine or others like the GM-CSF would ameliorate the toxicological profile of the treatment.	A3 A7 B3 B1 B2
Tisagenlecleucel	TA554	potential cure: novel treatment approach in which the patient's own immune cells are genetically reprogrammed so that they can recognise and fight the cancer, potentially for a lifetime. Only single infusion required. durable response, clinically meaningful improvements in HRQoL, and the potential for a cure in patients who would otherwise have a very poor prognosis.	A1 A8 B4
Tisagenlecleucel	TA567	no curative treatment options currently available that can offer long-term OS benefits, with treatment mainly given with palliative intent. novel treatment paradigm in which the immune system is harnessed to combat the disease. unmet need for new treatments that can offer durable responses and improve survival outcomes for patients with r/r DLBCL who have received two or more lines of systemic therapy	A1 D1 A8
Axicabtagene ciloleucel	TA559	innovative approach that provides complete personalised immunotherapy. single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy and their associated toxicity (results in 100% patient compliance). significant benefit in the potential treatment landscape for R/R DLBCL, PMBCL and TFL patients, who are ineligible to transplant and associated with a median life expectancy of 3.3 to 6.3 months. current treatment options for patients with R/R DLBCL, PMBCL and TFL ineligible for ASCT are extremely limited and generally consist of palliative care. patients with DLBCL who achieve event-free survival at 24 months following first-line immunochemotherapy treatment have a subsequent OS equivalent to that of the age- and sex-matched general population, which means these patients can be considered to be cured. offers patients a better chance of achieving remission where traditional chemotherapy has failed.	A8 B4 A7 B2 A5 A6 D1
Burosumab	HST8	no treatments that target the underlying cause of XLH. burosumab has the potential to eliminate the need for multiple daily doses of oral therapy while improving skeletal outcomes and overall mobility, essentially allowing the child and their family to have a more normal daily life while improving long-term outcomes. Burosumab is well tolerated and avoids complications that are associated with conventional therapies. Clinical expert opinion has suggested that patients responding well to burosumab treatment are likely to have a diminishing frequency of consultant visits over the longer term. In addition, burosumab will either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery. Routine treatment with burosumab should also remove the need for additional supplementation with growth hormone in a small subset of patients where this is required.	A8 B4 A5 C2 A7 B8 B9
Strimvelis	HST7	for about half of people with ADASCID, an HLA-matched related donor cannot be found. First-approved gene therapy. life-saving treatment with a 100% survival rate and highly successful engraftment rate. It is a one-time, single-dose therapy with the potential for long term or permanent benefit of immunological manifestations of ADA-SCID It is an autologous therapy, so there is no risk of GvHD or rejection due to HLA mismatching or minor antigen incompatibility	A6 A1 B4 A5

A.2 DATA EXTRACTION SCREENSHOT FOR FAD INNOVATION

Intervention	NICE ID	FAD agreed innovation	Code NICE themes
Bosutinib	TA401	The committee considered whether bosutinib was innovative and noted the company's comments that bosutinib has efficacy in patients whose CML is resistant to other tyrosine kinase inhibitors and that it has a good tolerability profile. The committee considered that the mutations that cause resistance to tyrosine kinase inhibitors differ and that some mutations cause resistance to bosutinib. Overall, the committee concluded that bosutinib did not offer a step-change from the tyrosine kinase class of drugs and that there were no additional benefits with bosutinib that had not been included in the QALY.	A6
Sofosbuvir + ribavirin	TA330	The Committee acknowledged that the marketing authorisation for sofosbuvir offers people theoption to receive shortened courses of peginterferon alfa and ribavirin, or in some circumstances to have treatment without peginterferon alfa, thereby reducing potential adverse effects with interferon-based therapy. Clinical experts considered sofosbuvir to be an important new treatment which will address an unmet need, particularly in people who have previously been treated but did not have a sustained virological response, in people whose condition has relapsed, or in people who have become re-infected after treatment. The Committee heard from the patient experts that the availability of sofosbuvir will encourage more people with hepatitis C to seek diagnosis and treatment. The Committee accepted that sofosbuvir is a valuable new therapy. It agreed that there were other benefits (such as relief of loss of cognitive ability in people with HCV) and public health benefits (such as reduced transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, would decrease the ICERs	A7 A6 C4 C7 D5
Ledipasvir-sofosbuvir	TA363	The Committee discussed whether ledipasvir–sofosbuvir could be considered innovative, and whether the company's economic analysis had captured all changes in health-related quality of life. The Committee agreed that compared with current treatment, ledipasvir–sofosbuvir offers oral, shortened, interferon-free treatment, which is particularly important to people, and a major development in the clinical management of chronic hepatitis C. The Committee therefore acknowledged that ledipasvir–sofosbuvir is a valuable new therapy for treating chronic hepatitis C. The Committee agreed that there were other benefits for people with hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV [see section 4.15], improved earning capacity) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs. However, the Committee noted that it had taken these potential benefits into account when considering the cost effectiveness of ledipasvir–sofosbuvir and concluded that its recommendations for each population remained unchanged	A3 B3 A7 A5 C4 C1 D5
Ombitasvir-paritaprevir-ritonavir (2D)	TA365	The Committee discussed whether 3D and 2D could be considered innovative, and whether the company's economic analysis had captured all changes in health-related quality of life. The Committee agreed that compared with current treatment, 3D and 2D offer oral, shortened, interferon-free treatments, which are particularly important to people, and a major development in the clinical management of chronic hepatitis C. The Committee therefore acknowledged that 3D and 2D are valuable new therapies for treating chronic hepatitis C. The Committee agreed that there were other benefits for people with chronic hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs. However, the Committee considered that it had taken these potential benefits into account in its conclusions on the cost effectiveness of 3D and 2D for each population.	A3 B3 A7 A5 C4 C1 D5
Eculizumab	HST1	Committee accepted that eculizumab is a step change in the management of aHUS and could be considered a significant innovation for a disease with a high unmet clinical need. The Committee acknowledged that the company had attempted to capture the benefits of treatment on extra-renal manifestations in the higher utility value assigned to the health states for those having eculizumab compared with standard care. Even with this, the Committee felt that it was likely that other benefits of a substantial nature had not been adequately captured in the model, and therefore may have led to the underestimation of the overall effectiveness of eculizumab	A2 A7 D5
Elosulfase alfa	HST2	The Committee concluded that elosulfase alfa improved various abilities and aspects of health compromised by the disease, and that the health and quality of life of some patients improved significantly on treatment. Before elosulfase alfa became available, there were no treatments that address the underlying disease.	A5 A2 A8
Nivolumab	TA384	The Committee noted that programmed cell death-1 (PD-1) receptor inhibitors such as nivolumab and pembrolizumab appear to have a faster onset of action and higher response rate than ipilimumab, and may also be more suitable for treating high-volume disease. The Committee agreed that the low toxicity and the favourable adverse effects profile of nivolumab compared with other treatments represent a promising new advance in immunotherapy for the treatment of metastatic melanoma. However, it could not identify any specific health-related benefit that had not already been captured in the QALY calculation	A5 A6 B2 A7
Ruxolitinib	TA386	The Committee considered whether ruxolitinib is an innovative treatment. It agreed that ruxolitinib provided a step change in treating splenomegaly and symptoms in people with myelofibrosis. The Committee acknowledged that ruxolitinib is a targeted treatment and manages symptoms for which there is currently no available treatment. Therefore, the Committee agreed that ruxolitinib is innovative, but there were no additional gains in health-related quality of life over those already included in the QALY calculations.	A4 A2
Lumaftor-ivacaftor plus SoC	TA398	In its submission, the company stated that lumacaftor–ivacaftor addresses an unmet need because it is the first treatment to specifically target the F508del mutation. The committee agreed that lumacaftor–ivacaftor offers people an oral treatment option that has the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. It recognised that this was particularly important to people with cystic fibrosis. The committee therefore acknowledged that lumacaftor–ivacaftor was a valuable new therapy for managing cystic fibrosis. It agreed that lumacaftor–ivacaftor has wider benefits to society for people with cystic fibrosis and carers of people with cystic fibrosis (for example, maintaining employment and improved family life). The committee understood from the company's response to consultation that the company considered that all the evidence for lumacaftor–ivacaftor had not been taken into account. However, the committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality-of-life effects had not been captured in its economic modelling. It agreed that direct health effects for carers had not been taken into account in the company's economic model as considered appropriate in NICE's guide to the methods of technology appraisal (2013). However, the committee concluded that even if the company's economic model had taken into account these uncaptured direct health effects, given the very high ICER for lumacaftor–ivacaftor plus standard of care compared with standard of care alone, its recommendation would remain unchanged.	A3 B4 A7 B3 B5 C1 C2 D5
Elbasvir-grazoprevir	TA413	significant unmet need in people with chronic hepatitis C complicated by severe renal disease. The committee noted that like some of the newer treatments for chronic hepatitis C, the dose of elbasvir-grazoprevir does not need to be adjusted for any stage of renal impairment. The committee also recognised the additional value of elbasvir-grazoprevir as an interferonand ribavirin-free treatment but concluded that these health gains are likely to have been included in the QALY calculations. The committee agreed that there were other wider benefits to society (for example reduced transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs. However, the committee noted that it had taken these potential benefits into account when considering the cost effectiveness of elbasvir-grazoprevir and concluded that its recommendations for each population remained unchanged.	A6 B4 A7 C4 D5
Ataluren	HST3	The committee heard from the clinical experts that, because ataluren potentially addresses the nonsense mutation that causes DMD to develop, they considered it to be a step change in the management of DMD. The committee agreed that ataluren was an innovative treatment and would be likely to stimulate further research in this therapy area.	A8 A2 C3
acid + ursodeoxycholic acid	TA443	committee accepted the innovative nature of the treatment, and considered that this was a major change in the management of PBC. The committee noted in particular that the results in 47% of people in the obeticholic acid arm of POISE met the strict criteria for response, despite the current standard of care, ursodeoxycholic acid, not having been effective. This response would be associated with a very favourable prognosis.	A2 A5
Reslizumab as an add-on therapy	TA479	The committee heard from stakeholders that reslizumab is innovative in its potential to make a significant and substantial effect on health-related benefits. The committee heard from the clinical experts that there are few treatments for severe eosinophilic asthma that have the potential to reduce corticosteroid use. It noted that it had not seen any evidence on preventing or delaying the use of maintenance oral corticosteroids but heard from the clinicians that this is an important aim of treatment with reslizumab. The committee agreed that some benefits related to avoiding the significant adverse effects of oral corticosteroid use had not been fully captured in the QALY calculations. The committee also considered that there were benefits to carers, which may not have been captured in the QALY calculation. The committee therefore agreed that reslizumab could be considered innovative.	A5 B3 A7 D5 C2
Asfotase alfa	HST6	The committee acknowledged that asfotase alfa offers a lifeline for babies with paediatric-onset hypophosphatasia, who would otherwise die. The committee heard from the clinical experts that, because asfotase alfa was the first therapy that specifically targets the underlying cause of hypophosphatasia, they considered it to be a step change in the management of paediatric-onset hypophosphatasia.	D2 D1 A2 A8
Glecaprevir-pibrentasvir	TA499	The committee considered whether glecaprevir–pibrentasvir could be considered innovative, and whether the company's economic analysis had captured all associated health-related benefits. The committee agreed with the company that there is an unmet need for interferon-free regimens to treat people with previously treated genotype 3 hepatitis C, particularly those with severe renal impairment. However, the committee concluded that it had taken these potential benefits into account when considering the cost effectiveness of glecaprevir–pibrentasvir. Pan-genotypic regimen may contribute to reduced equality concerns, potential to remove the requirement to genotype any TN NC patients.	A7 A6 C6 B7
Sofosbuvir-velpatasvir-voxilaprevir	TA507	The committee considered whether sofosbuvir–velpatasvir–voxilaprevir could be considered innovative, and whether the company's economicanalysis had captured all associated health-related benefits. The committee agreed with the company that there is an unmet need for people who have had unsuccessful treatment with DAA. However, the committee concluded that it had taken these potential benefits into account when considering the cost effectiveness of sofosbuvir– velpatasvir–voxilaprevir.	A6
Dinutuximab beta (APN311)	TA538	[From committee papers NICE slides] Dinutuximab beta Apeiron's main benefit stands in its continuous infusion scheme, which shows major improvements of the safety profile by reducing pain and associated i.v. morphine use • Together with the possibility of receiving the treatment in outpatient setting, will facilitate patients remaining on therapy and receiving the full cycle of treatment, optimizing the possibility of long-term benefits	A3 A7 B3 B1 B2
Tisagenlecleucel	TA554	The committee considered tisagenlecleucel to be innovative because it represents a step-change in the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia. The company's submission stated that substantial positive effects for patients and caregivers, such as allowing return to work or employment, had not been captured in the economic analysis. The committee was mindful that the effect of tisagenlecleucel on employment were outside NICE's reference case, which specifies that the costs and benefits of a technology should be considered from the perspective of the NHS and personal social services. It noted that tisagenlecleucel was granted eligibility as a priority medicine through the European Medicines Agency's PRIME scheme. The committee concluded that there are no additional benefits that had not been captured in the economic analysis.	A2 C2 C1 D5 D3
Tisagenlecleucel	TA567	The committee considered tisagenlecleucel to be innovative because it represents a step change in the treatment of relapsed or refractory diffuse large B-cell lymphoma. It noted that tisagenlecleucel had been designated as a priority medicine (PRIME) by the European Medicines Agency. The company did not present any evidence to suggest that there were additional benefits that were not captured in the QALY calculations. The committee concluded that there were no benefits not captured in the analysis.	A2 A6 D3
Axicabtagene ciloleucel	TA559	The committee considered axicabtagene ciloleucel to be innovative because it represents a step-change in the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large Bcell lymphoma. It noted that axicabtagene ciloleucel was granted eligibility as a priority medicine through the European Medicines Agency's PRIME scheme. In response to consultation, NHS England and the patient organisations reiterated that axicabtagene ciloleucel is an innovative treatment and the transformative nature of treatment required further consideration by committee. The committee acknowledged that axicabtagene ciloleucel was considered a step-change and agreed to consider this in its decision-making. However, the company did not present any evidence to suggest that there are additional benefits that were not captured in the QALY calculations.	A2 A6 D3
Burosumab	HST8	The committee recognised that burosumab was the first treatment that inhibits the action of excess FGF23, so affecting the pathophysiology of XLH. It also acknowledged comments from patient and clinical experts that the administration of burosumab is less burdensome than current treatment options. It agreed that this was a benefit of the treatment but did not represent an innovation. The committee concluded that burosumab was innovative in its mechanism of action, but not in its administration. The clinical and patient experts explained that burosumab was expected to be associated with a reduced need for surgical intervention. The committee recalled that surgical intervention was distressing and disruptive to children and parents (see section 4.2), and heard that repeated surgeries would be costly to the NHS. The committee was concerned that the health benefits from avoiding surgery had not been fully captured within the vignette study, and that the cost impact had also not been fully captured in the model. It considered any reduction in the need for surgical intervention could represent a significant benefit to people with XLH. It agreed that fully including these benefits in the model would favour burosumab and subsequently reduce the ICER. The committee agreed that long-term monitoring of surgical intervention would allow a quantitative assessment of these benefits.	A8 B4 B8 C2 D5
Strimvelis	HST7	The committee considered the innovative nature of the technology. It noted that, to date, Strimvelis is the only ex vivo gene therapy to gain marketing authorisation from the European Medicines Agency. The company considered that Strimvelis is a step-change in managing ADA– SCID because it corrects the underlying cause of the condition using the patient's own cells, circumventing the need for a stem cell donor search and the risk of immune rejection (GvHD). The committee concluded that Strimvelis was an innovative technology. The committee also noted that there were several health-related benefits and wider benefits of Strimvelis treatment that were not captured in the economic analysis, and recognised that Strimvelis is an innovative technology. The committee concluded that, although Strimvelis was a high-cost technology and uncertainties remained in the clinical evidence, it is likely to provide important clinical benefits for people with ADA–SCID at a cost that is manageable and value for money in the context of a highly specialised service.	A2 A8 B9 A7 D5 A5