A scoping review of patient and public perspectives on cell and gene therapies

Macpherson, Karen ; Aiyegbusi, Olalekan Lee; Elston, Lauren ; Myles, Susan ; Washington, Jennifer ; Sungum , Nisha ; Briggs, Mark ; Newsome, Philip; Calvert, Melanie

DOI:
10.2217/rme-2020-0181

A scoping review of patient and public perspectives on cell and gene therapies

Karen Macpherson[1], Olalekan Lee Aiyegbusi[2,3,4], Lauren Elston[5], Susan Myles[5], Jennifer Washington[5], Nisha Sungum[6], Mark Briggs[7], Philip Newsome[4,6], Melanie Calvert[2,3,4,8]

1. Healthcare Improvement Scotland, Glasgow, UK

2. Centre for Patient Reported Outcome Research, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

3. National Institute for Health Research, Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, UK

4. National Institute for Health Research (NIHR) Applied Research Centre West Midlands, University of Birmingham, Birmingham, UK

5. Health Technology Wales, Cardiff, UK

6. University Hospital Birmingham NHS Foundation Trust

7. Velindre University NHS Trust

8. National Institute for Health Research Surgical Reconstruction and Microbiology Research Centre, University of Birmingham, Birmingham, UK

Structured abstract (maximum 120 words)

Aims

The development and introduction of cell and gene therapies presents complex social and economic issues. Fully addressing these challenges requires engagement with patients and the public.

Materials and Methods

A systematically conducted scoping review was undertaken to gauge current patient and public knowledge and perspectives, and as such inform requirements for future research, education and engagement activities.

Results

A heterogeneous collection of 35 studies were identified. Levels of knowledge among patients and the public were extremely variable. Studies indicated general acceptance of therapies.

Conclusions

The review identified the need for tailored educational activities, and in particular the importance of addressing misconceptions. There is also a need for robust qualitative research considering perspectives on current and forthcoming licensed therapies.

Keywords

Cell and tissue based therapy; Genetic therapy; Patient preference; Health knowledge, attitudes, practice; Health education; Public opinion

Introduction

Novel cell and gene therapies, defined within the European Union as Advanced Medical Therapy Products[1, 2], offer ground-breaking opportunities to treat disease and to restore function, and in some instances are curative. For example CAR (chimeric antigen receptor) T-cell therapy has been used to treat certain adults with lymphoma[3], and other cell therapies are also being considered for applications in indications ranging from immune disorders to circulatory and heart conditions[4], gastroenterology[5] and neurological conditions[6]. Gene therapy has been offered to patients to halt disease progression in a particular inherited retinal disorder (Leber congenital auaurosis), and similarly to cell therapy is being studied for application in a wider range of clinical areas[7]. However these therapies pose new and complex logistical, social, ethical, health and economic issues, as well as risks to patients such as life threatening toxicities[8]. There is a need therefore to engage with, educate and to raise awareness of these therapies with the public, in their role as the funders of national health systems, and the future potential recipients of these therapies as patients. Awareness and understanding of cell and gene therapies among patients and the public will enable their contribution to policy debate, enhance their ability to make informed decisions about participation in clinical trials of new therapies, encourage them to accept the integration of these new therapies into routine clinical practice, and to advocate for affordable equitable provision.

The Advanced Therapies Treatment Centres (ATTCs)^ have been set up within the UK National Health Service (NHS) framework, to bring together the NHS, academia and industry to address the unique and complex challenges of bringing these therapies to patients. To guide the work of the programme with respect to patient and public engagement, information was required on what the patients and public currently know and understand about cell and gene therapies, and what is their perspectives on these.

An initial exploration of published literature did not identify any systematic reviews that synthesised literature on patient and/or public knowledge or perspectives of cell and gene therapies, or reviewed engagement methods with patients and/or public on these therapies. Published primary studies addressing different aspects of this area of interest were however identified, and it was considered that bringing these studies together in a systematic manner would provide a useful reference source to inform future activity, both within the UK health service setting, but also internationally. The apparent heterogeneity of these studies in terms of the populations considered, research methods employed, study settings and time periods covered suggested that it would be inappropriate to use quantitative and/or qualitative techniques to synthesise this literature; however systematic methods could be used to map out the available evidence in the form a scoping review[9].

The aim of the scoping review was to describe published research studies and their findings in relation to the following question:

> *What are the perspectives of patients, carers' and the public on cell, gene and tissue engineered therapies as novel therapeutic options becoming available within healthcare systems?*

This overall question was subdivided into a series of sub-questions to guide the identification of relevant literature:

1. *What do patients, carers' and the public know and understand (how they interpret that knowledge) about cell, gene and tissue-engineered therapies, including their risks and benefits?*
2. *What are patients', carers' and the public's expectations and hopes of treatment with cell, gene and tissue-engineered therapies?*
3. *What are patients', carers' and the public's experiences of treatment with cell, gene and tissue-engineered therapies?*

4. *What do patients, carers' and the public think about the availability (including reimbursement/prioritisation/geographical provision) of cell, gene and tissue-engineered therapies?*

5. *What can influence and/or change carers', carers' and the public's attitudes to cell, gene and tissue engineered therapies?*

It should be noted that 'carers' in the research question and all the sub-questions relates only to informal unpaid carers such as friends and family.

Methods

The research question and sub-questions were translated into concepts according to the PICO framework as illustrated in Table 1, and this was used to inform the design of the search strategy and determine inclusion and exclusion criteria. While the PICO format is commonly used for defining the concepts for search strategies for systematic reviews of intervention studies, it was still felt to be applicable for the current work given the comparison to be made with standard care, and considering patient preferences and views as outcomes. The PCC (Population, Concept, Context) framework could also be used. Systematic searches were undertaken between January and March 2019 to identify relevant research studies, published in English, from January 2009 to March 2019. The search strategies were developed through an iterative process which included adapting the SIGN (Scottish Intercollegiate Guidelines Network) Patient Issues filter (https://www.sign.ac.uk/search-filters.html). No restriction by study design was applied, but studies using health economic techniques to elicit patient and public preferences, such as discrete choice methods, were not sought as these are being captured in a separate systematic review on methodological approaches to conducting Health Technology Assessment (HTA) of Advanced Therapy Medicinal Products[10]. As the aim of this work was to collate robust and transparent research-based evidence, narrative reviews not based upon systematic searches were excluded, as were commentaries, opinion pieces and letters. Given the anticipated limited amount of conventionally published research literature in this area, conference abstracts as well as full peer reviewed publications were included where they contained sufficient information on the PICO characteristics of the study to be useful. The bibliographies of all included studies were scanned to identify any additional relevant references not identified by the search strategy. The search dates were based upon the timing of the issuing of EU legislation on ATMPs (Regulation (EC) No 1394/2007) and the subsequent updating of the EU ATMP definitions (Commission Directive 2009/120/EC). Also, the rapid pace of development in this area suggests that more recent literature will be most relevant so it was not felt necessary to search literature published prior to 2009. Scoping searches did not identify any seminal work published prior to this time.

Full details of the literature search are available in Appendix 1. The databases searched were as follows:

- Medline
- Embase
- CINAHL
- PsychINFO
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- DARE
- HTA database
- Current Controlled Trials
- Prospero database

Relevant studies were selected according to the characteristics outlined in Table 1.

Table 1: PICO characteristics

Population	People with a health condition who have received, or may be eligible now or in the next few years to receive, a novel cell or gene therapy; Informal carers; Members of the public.
Intervention(s)	Cell, gene and tissue engineered therapies either in clinical application or being currently considered within clinical trials.
Comparator(s)	Current standard care.
Outcomes	Levels of knowledge, understanding and awareness of these therapies; Expectations or hopes for these therapies Experiences of treatment with these therapies Views, attitudes and perspectives towards these therapies Changes in views attitudes and perspectives towards these therapies, including sources of influence.

Given the goal of this work was to inform international practice in relation to forthcoming licensed therapies, the review focussed on the cell types and processes used within these particular therapies. As such, publications were excluded if their focus was upon:

- the use of human embryo cells
- use of cells in therapies that are well established and where substantial manipulation of the cell is not required, such as hematopoietic stem cell transplants to replenish bone marrow or blood cells, following oncological treatment or similar
- germline gene therapy
- use of any therapies to enhance or prolong life in the absence of any clinical indication
- unlicensed therapeutic use of the therapies

Citations were downloaded into Endnote® software (version X9) and duplicates deleted. The screening process was conducted independently be two reviewers (KM 100% of records (10,735) and OLA a 20% sample). Records were screened by considering their titles, abstracts and their indexing terms. Potentially relevant articles were identified for further full-text screening (KM and OLA both considered all articles). Discrepancies were resolved through discussion and recourse to a clinical advisor (MB). A data extraction form was piloted for use by the two main researchers on three studies, and then data extraction undertaken by these two authors plus two other members (LE, SM) of the research team. Variables extracted included date of the study, where it was conducted, the method followed, characteristics of participants such as age, education levels, and type of therapy considered. Full details are available from the authors on request. A formal synthesis of these studies was not undertaken; rather the studies were categorised according to the population and therapy studied, and described. These descriptions were then mapped to respond to the five research questions, with a narrative summary of the relevant study findings presented. Formal consultation with stakeholders was not undertaken but the work was discussed with a steering group of experts at various stages of the development process.

Results

On initial review, 151 papers were selected for full-text review, and on more detailed consideration, 118 of these were deemed not to meet the inclusion criteria for the review (mainly because they were not based upon research studies, because they focussed upon hematopoietic stem cell transplants, or because they were concerned with therapies that are not in current clinical application or being currently considered within clinical trials), and excluded. This left 38 papers as potentially suitable for inclusion. References lists

of these 38 studies were scanned to identify any additional relevant studies. Two additional references were included as a result of this, giving 40 studies potentially suitable for inclusion. Following data extraction, five studies were deemed not to meet the inclusion criteria and excluded from this review. Reasons included the paper being a discursive piece rather than a research study and the therapy being considered not meeting the inclusion criteria for this review. This left 35 studies to be included in the scoping review. The included studies are listed in Table 7, in Appendix 1.

A PRISMA diagram[11] showing the study selection process is provided in Figure 1 in Appendix 1.

Description of the included studies

Tables 2 to 5 provide summary details of the included studies in terms of participants, type of therapy considered, study setting and methods of data collection

Table 2: Participants

Participant groups included in studies	Number of studies	References
Patients only	9	[12-20]
Patients and public	2	[21, 22]
Patients and carers/friends/ family	4	[23-26]
Patients, carers and the public	1	[27]
Patients, carers, clinicians and patient advocates	2	[28, 29]
Public only	12	[30-41]
Public alongside clinician or scientists views	2	[42] [43]
Firefighters	1	[44]

Three studies looked at media representation and perception through newspapers [34, 45, 46].

Table 3: Type of therapy

Intervention considered in study	Indication considered	Number of studies	References
Gene therapy	None specified	5	[35, 36, 39, 41, 42]
	Choroideremia	1	[28]
	Genetic eye disease	1	[15]
	Cystic fibrosis	1	[18]
	Duchenne muscular dystrophy	1	[24]
	Sickle cell disease	1	[16]
Stem Cell therapy	None specified	13	[27, 29-34, 37, 38, 40, 43, 45, 46]

	Generally and 15 specific disorders	1	[19]
	Stroke	3	[12, 13, 23]
	Burns	2	[20, 44]
	Spinal cord injury	2	[14, 25]
	Cancer	1	[22]
	HIV/AIDs	1	[21]
	Pakinson's disease	1	[26]
	Post-obstetric incontinence	1	[17]

Table 4: Study setting

Where the study was conducted	**Number of studies**	**References**
United Kingdom	5	[17, 18, 23, 32, 38]
United States	8	[16, 21, 24, 31, 33, 37, 40, 41]
Canada	6	[25, 27, 28, 36, 44, 45]
Australia	2	[19, 29]
Belgium	1	[22]
China	1	[42]
Germany	1	[15]
Hungary	1	[46]
Ireland	1	[20]
Japan	1	[43]
Korea	1	[26]
South Korea	1	[12]
Sweden	1	[13]
Multiple European countries	1	[39]
Canada and USA	3	[14, 34, 35]
Europe, USA and Canada	1	[30]

Table 5: Methods of data collection

Data collection method used in study	**Number of studies**	***References***
Questionnaires/polls	15	[13, 17, 19, 20, 22, 26, 30, 33, 35, 38-43]
Focus groups	5	[16, 21, 23, 27, 31]
Interviews	6	[12, 14, 18, 24, 28, 29]
Questionnaires followed by semi-structured interviews	2	[15, 44]
Focus groups and interviews	2	[25, 32]

Five studies performed content analysis. The three studies that looked at media representation used content analysis of news media articles either alone[45], with readers' comments[34] or with perceptions from focus groups[46]. One study analysed questions and answers from a website (Yahoo! Answers)[36] and the other analysed consultation comments on a US FDA guidance document[37].

Narrative synthesis

Table 6 summarises the main findings derived from mapping the included studies to the research questions and undertaking a narrative synthesis of these study results

Table 6: summary of key findings

Question	Findings
1. ***What do patients, carers and the public know and understand about cell, gene and tissue engineered therapies, including their risks and benefits?***	- there are varying levels of knowledge and understanding among patients, with variation across indication but also within indications over different population groups and study dates - some associations seen with patient characteristics such as age and gender, but this was not consistently studied - the desire to know and understand more also varied among patients - limited research relating to members of the public and very little undertaken with informal carers
2. ***What are patients', carers' and the public's attitudes to, and expectations of, treatment with cell, gene and tissue engineered therapies?***	- levels of acceptance of cell and gene therapies among patients varied, but particularly after information on the therapies was supplied, generally were fairly high - some associations seen with patient characteristics, but this was not consistently studied - in very general terms there appears to be good acceptance of these therapies amongst the public - some variance in this over time/region/source of cells/indication
3. ***What are patients', carers' and the public's experiences of treatment with cell, gene and tissue engineered therapies?***	- no studies identified which examined experiences in populations currently receiving, or having received a licensed cell or gene therapy product. Only studies considering hypothetical treatment
4. ***What do patients, carers and the public think about the availability (including reimbursement/prioritisation/geographical provision) of cell, gene and tissue engineered therapies?***	- no studies specifically considered patient views on reimbursement, prioritisation or geographical variation in provision - the public expressed some views about the cost of the therapies to the healthcare system, and how accessible these would be for the less well-off members of society however in general, studies either did not ask about these issues or they were not raised by participants
5. ***What can influence and/or change patients', carers' and the public's understanding of and attitudes towards cell, gene and tissue engineered therapies?***	- patients wished for more, particularly personalised, information - nature of the interaction with clinicians has an impact

	- overly positive perspectives held by patients and public may be influenced by media portrayal - campaigning groups and political events can also exert an influence

1. ***What do patients, carers and the public know and understand about cell, gene and tissue engineered therapies, including their risks and benefits?***

Studies conducted with patients indicated varying levels of knowledge and understanding of cell and gene therapies[12, 13, 15, 16, 18, 19, 21]. A small study of patients with a genetic retinal deficiency indicated that they felt well informed about gene therapy[15]. 150 pregnant women in Australia reported that overall, their self-assessed knowledge of cell therapy among was high, with 78% reporting to be reasonably confident about their knowledge of stem cell therapy, and only 5% reporting no understanding [19]. In other larger studies, levels of knowledge were lower, but these varied by indication. King et al found that in focus groups conducted in the US with individuals who were HIV positive, approximately 60% of participants were aware of the potential application of stem cell research to treat Parkinson's disease, and sickle cell anaemia, but only 28% were aware of its potential in HIV/AIDs treatment [21]. There could also be variations for the same indication across studies considering different populations, undertaken at different times or using different methods. A survey in Sweden by Aked et al[13] found a low level of awareness of stem cell therapy among 84 patients (aged between 20 and 75 years) who had experienced their first ever ischaemic stroke. Only 12% of patients had any knowledge of cell therapy prior to being offered instructional material. Kim et al[12] administered a questionnaire to 250 patients in South Korea with chronic ischaemic stroke (mainly male, with mean age of 63 years). 48% had previously heard of cell therapy and 35% were aware that cell therapy trials were underway internationally.

Age, gender and education levels were characteristics shown to be associated with perceived levels of knowledge in some studies. For example, Strong et al in a survey of adult patients attending a sickle cell disease (SCD) treatment centre in the US, found that 38% of patients aged 18 to 30 and 56% of older patients reported being aware of gene therapy as a potential treatment for SCD[16]. Nelissen et al., in a regression analysis of data from a cancer information survey undertaken in Belgium, showed that men and individuals with higher educational degrees had higher levels of knowledge about stem cells[22]. However, such associations were not seen consistently across studies. In the Hodges et al study[19] with pregnant women, there was no statistically significant differences in confidence in their level of knowledge between women with, and without, tertiary education.

Patients were seen in some studies to be uncertain about sources of cells, the chances of catching disease from the cell donor, about the use of viral vectors and their likelihood or otherwise of transmitting infection, and the, risks of concomitant chemotherapy[16].

The extent to which patients wanted to know more or understand more about their therapy varied considerably across studies, and patient groups. In a study of 47 individuals with HIV, all study participants indicated that they wished more information about stem cell and gene therapy[21]. Individuals with spinal cord injuries who were interviewed in a research study in Canada, wanted to learn more about stem cell therapy, but many had not discussed it with their clinicians. Some felt that their clinician would not have the knowledge or willingness to engage in such discussions[14]. Jannetta in semi-structured interviews with 12 patients with cystic fibrosis who were involved in the preparatory phases of a gene therapy trial in the UK, found that while a small number of the participants had some understanding of gene therapy, none fully understood it. The participants felt that they did not need to fully understand the science behind the

therapy as they had confidence in the advice from their healthcare facility, the skills of the research team and the findings of previous studies[18].

There was very little research identified on the levels of knowledge and understanding of family, friends and informal carers of patients.

Studies examining the knowledge and understanding of members of the public covered a variety of different aspects of the broad topic of cell and gene therapy, such as ownership of donated material[31], regulatory processes[37, 39], and sources of cells[27]. There was little consideration of levels of knowledge per se, rather discussion of view-points on particular issues, which may indirectly indicate the knowledge held by the participant. One study suggested that the information that professionals wish to convey may not be the information that patients or the public is looking for. In a questionnaire study conducted in Japan, Shineha et al. found that professionals focussed on scientific content and validation, and the current lack of clinical trials. However the public's primary interest was related to the consequences of possible success of the new the therapies, such as their cost and the treatment available in case of accidents[43].

2. ***What are patients', carers' and the public's attitudes to, and expectations of, treatment with cell, gene and tissue engineered therapies?***

Levels of acceptance of cell and gene therapies among patients varied, but particularly after information on the therapies was supplied, generally were fairly high[17, 20, 26]. Age[16], gender[12, 13] and education level[22] were all seen in some cases to be an influence on willingness to accept the therapies, with older adults, men, and those with higher levels of education, being more accepting. Likewise, the perceived risk/benefit balance of therapies[17, 24], severity and level of progression of the underlying condition[12, 19, 23, 26, 47] and also the type and source of cells being used[19], were associated with acceptance. However, these associations were not consistent across studies, and few studies were set up to robustly assess statistical significance of associations, enabling more definitive conclusions to be drawn.

Study design can also influence patient's attitudes, as some patients were seen to be less keen to participate in placebo controlled trials compared with single arm trials, as they could only guarantee getting their own cells in a single arm trial [37]. In a number of studies, it was seen that patients tended to overestimate the benefits that cell and gene therapies may offer, particularly around whether the therapies would be disease-limiting or disease-reversing[12, 15, 23, 28]. Some patients were so concerned about gaining access to therapy, that they showed limited concern for side effects[12, 28]. There were also unrealistic expectations around the timescales for the availability of actual therapeutic options[18]. Some patients were less sanguine about the timescales, but still keen to participate in research studies for altruistic purposes[16].

As was the case when thinking about levels of knowledge and understanding of members of the public, the studies looking at attitudes of the public towards cell and gene therapies covered a diverse range of aspects of the topic. In order to examine the nature and range of perspectives they often drew on a variety of different population groups. As such, there is much heterogeneity in this evidence, and drawing out clear messages is challenging. In very general terms there appears to be acceptance of these therapies amongst most population groups[27, 30, 35, 36, 40, 41, 43, 44]. Attitudes are seen to vary over time[33, 35], across geographic regions[30, 39], in relation to different sources of cells[27, 40] and usage in different indications[35, 36, 42]. For example, Robillard et al. found when asking members of the public in north America to complete an online survey, that respondents' acceptance of gene therapy was higher for conditions perceived to be more severe[35]. In an ethnographic study conducted in Scotland, researchers found that whether cultured red blood cells were positioned as 'natural' or 'synthetic', would impact their uptake across different groups of individuals[32]. There is also some variance evident in some studies by gender, age, religious belief, marital status, education level, employment status, risk perception and rural versus urban participants[35, 39, 42]. However, the nature of the studies means that these associations can only be considered exploratory. Appropriate regulation is important to the public[43] and what is

considered appropriate varies[37]. An attitude of altruism is apparent in some studies[31, 38], with a view that taking part in trials is important to benefit the future generation. A study of queries posed by members of the public using social media, indicated high expectations for gene therapy that did not reflect the current reality[36].

3. ***What are patients', carers' and the public's experiences of treatment with cell, gene and tissue engineered therapies?***

   No studies were identified which examined experiences in populations currently receiving, or having received a licensed cell or gene therapy product. All studies were either in populations potentially eligible to receive therapy in future, or being offered therapies as a hypothetical construct. As more therapies are considered for reimbursement decisions by Health Technology Assessment bodies, many of whom place value in the perspectives on patients in decision-making, such material may start to become more widely available.

4. ***What do patients, carers and the public think about the availability (including reimbursement/prioritisation/geographical provision) of cell, gene and tissue engineered therapies?***

   No studies specifically considered patient views on reimbursement, prioritisation or geographical variation in provision of these therapies.

   Within the studies conducted with members of the public, there were some views expressed about the cost of the therapies to the healthcare system, and how accessible these would be for the less well-off members of society[27, 43, 46]; however in general, studies either did not ask about these issues or they were not raised by participants.

5. ***What can influence and/or change patients', carers' and the public's understanding of and attitudes towards cell, gene and tissue engineered therapies?***

   Patients frequently indicated a desire for more information to inform their understanding[21, 29]. For example, they wanted to see results from large, long-term studies, and explicit reporting of risks and side effects observed in these studies[16]. They also expressed a need for more personalised information on whether they may be eligible or not for particular trials. The importance of the patient/clinician interaction and perceived knowledge of the clinician by the patient was discussed in several studies[13, 14]. Some of these showed that when patients were offered information about stem cell therapy, they were more likely to be accepting of the therapy, but in other cases, patients felt less positive about therapy when finding out more about side effects[13, 16]. The nature of the material that patients are presented with can also influence their acceptance of it[16]. Honesty in provided information is highly valued[16].

   Television is a major source of information on the novel therapies for patients[12, 13]. Also commonly cited as providing information were newspapers and magazines, the radio, clinicians, friends and colleagues. Clinicians were perceived as the most reliable source of information by a group of patients who had experienced ischaemic stroke[12]. The overly positive views held by some patients may be coming from inaccurate media portrayals of outcomes achievable, and the need for a balanced presentation of information to counteract this was therefore highlighted as important[23]. Likewise, the media often conflates use in research with use in clinical practice, and thus does not convey that trials are experimental, with no guarantee of benefit, and with risk of harm. There is a need to clarify the distinction for patients[28].

National political events may influence the views of the public and as such result in views changing over time[33]. Views can also alter in response to changes in the ethical and moral beliefs held in wider society, and greater awareness of the risks and benefits of therapies[30]. This indicates the need to regularly examine public views. Campaigning groups are a further potential source of influence[37]. The positioning of a product, in the example studied describing red blood cells as 'cultured' or 'synthetic', is seen to influence the level of acceptance of it by the public [32].

The impact of the media on public perspectives was examined in a couple of studies[34, 46]. Media coverage often has a particular slant, such as lack of wider availability of these therapies, or reporting specific breakthroughs or safety incidents, and this appears to influence the responses received to that coverage[34]. However, it is acknowledged that it is difficult also to disentangle the extent to which the media is reflecting views, from the extent to which it is influencing these views. A disconnect between the media portrayal of levels of stem cell therapeutic development and the clinical reality, may be fuelling an overly optimistic view of benefits achievable and timescales for these benefits [45].

Discussion

This scoping review provides a summary of patient and public perspectives of cell and gene therapies, as novel therapeutic options that are becoming available within healthcare systems. It indicates varying levels of understanding among patients and the public of the therapies, their anxieties and fears, but also strong, and sometimes overly optimistic, hopes and expectations. There is a general acceptance of the therapies, but within the context of limited knowledge. No consistent patterns across demographic groups, indications or therapies emerged, indicating both the complexity of this area, and also a need to tailor future knowledge and information sharing activities to specific groups and situations. The body of literature is larger than may have been expected for a relatively recent field of enquiry. Identifying and describing this evidence is considered to have created a valuable resource from which to build future engagement and research activities.

It is clear that the available research was produced over a wide time-period, with varied inclusion criteria, is of mixed methodological quality, and spans a wide variety of cultural and socio-political contexts. The decision to produce a scoping review rather than attempt to synthesise evidence in a systematic review is justified on these grounds.

The rigour applied to searching for and selecting studies for inclusion makes it likely that the majority of key research studies have been included. However there may be reports that consider patient and public perspectives that are not within peer reviewed publications and which have subsequently not been identified and/or included. For example, reports from governmental institutions, think tanks and research institutions. Given this is the first 'map' of the evidence in this area, it was considered appropriate to focus on identifying research papers initially. Only studies published in English were included so there may also be studies available in other languages. Future review work should include the wider 'grey literature', and also consider studies published in languages other than English.

Approximately two thirds of the studies identified relate to cell therapies, and the rest, gene therapies, so the results focus on these two types of advanced therapy. Only one study involved a tissue- engineered therapy, but its focus was upon the source of cells for the tissue engineering. Consequently, it is not possible to draw any conclusions in relation to that group of advanced therapies. Also, none of the studies identified considered currently licensed cell and gene therapies, so it must be borne in mind that the results relate to experimental use of therapies. As therapies start to be considered by Health Technology Assessment bodies such as the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium in the UK, and other similar bodies internationally, which place value on including the perspectives of patients in decision-making, such material may start to become more widely available. In a number of the studies, and particularly those looking at media representation of advanced therapy

related issues, it appeared that little distinction was made by study participants between their experimental use within research studies, unlicensed use in practice and licensed health system approved use. There was very limited discussion within the included studies on the economic and financial implications of these novel therapies, or to their potential impact on inequalities. It cannot be assumed however that these are not issues of importance or interest to the patients and public; it may be that the appropriate questions were not asked to elicit this information, or levels of knowledge and awareness are currently too low for views on these issues to be expressed. This would reflect the lack of penetration of these technologies into use, within official health systems, at this time.

While the review excluded sources of cells such as human embryos, and also was focussed upon the therapeutic use of cell and gene therapies rather than their use in research, participants may not have made these distinctions. In a number of studies, particularly those looking at media representation of advanced therapy related issues, it appeared that little distinction was made by study participants between experimental use within research studies, unlicensed use in practice and licensed health system approved use. The nature of qualitative enquiry means that while the included study aims were in line with the specified inclusion criteria, the responses gained may have strayed outside these limits. This makes interpretation of findings more complex, but is likely to reflect actual patient and public reactions in future, where these distinctions are unlikely to be clear to them.

This review has focussed upon the views of patients and the public. Another key influence upon uptake and acceptance of ATMPs are the attitudes and behaviours of healthcare staff and future work would wish to consider these too.

Conclusions

As anticipated, the literature in this area has proven to be heterogeneous in terms of methodology employed, participants studied, interventions considered and contextual factors. This scoping review, by setting out the available evidence, indicates current levels of knowledge and understanding on the topic, and can thus be used to guide future work. A number of suggestions can be made for primary research and to inform the conduct of patient and public engagement activities in relation to cell and gene therapy development. When further primary studies have been published, a future systematic review should be undertaken to bring studies together, which consider perspectives of similar participants, in relation to similar aspects of similar interventions.

Research recommendations

-Knowledge and understanding

- Following recent licensing of certain novel cell and gene therapies, current levels of knowledge and understanding among patients and the public should be studied, and monitored over time. The research could also start to interrogate areas of previously identified uncertainty such as source of cells, autologous versus allogeneic cells, use of viral vectors, awareness of safety issues and risks. The influence of the media should also be considered.
- Demographic characteristics of participants should be taken into account when planning studies and analysing results.
- The reasons for the mismatch between what patients want to know, and the information that professionals impart, would repay further investigation.

-Expectations and hopes

- Research is required which uses robust qualitative methods to understand the expectations and hopes of patients receiving, or about to receive, licensed cell and gene therapies.

- To understand patient preferences for use of cell and gene therapies versus standard management, studies using economic preference elicitation techniques[48] could be undertaken.
- Given the potentially large support role that informal carers, family and friends may have to assume, their needs, and views would repay greater investigation using robust qualitative methods.

-Experiences

- As patients start to receive the newly licensed therapies, patient experience data should be gathered at multiple time points, prior to, at and following the initial administration of the therapy.

-Availability

- Investigation into how patients and the public regard the use of highly expensive but potentially curative therapies for a limited number of patients, versus cheaper but non-curative therapies for a larger number of patients is needed. Methods used, and lessons learned, from studies attempting this in related areas of healthcare, such as medicines for rare diseases[49], could be employed to gather this data.

-Influencing and changing understanding and attitudes

- Testing of specific methods, material and content for raising knowledge and understanding with the groups to which it is to be targeted, is required. Social media, as a tool for gathering perspectives, as a source of potentially correct or incorrect information, and as a dissemination route, is likely to be a key component in this testing. Work is also required with and social care professionals to establish how best to ensure that they are in a position to inform prospective patients.

Recommendations for engaging with patients and the public

- Material needs to be tailored to different groups, the introduction of these therapies needs to be set within the context of existing management strategies and pathways, and there needs to be awareness of the role of conventional and social media. Focus also needs to be upon alignment of the messages that patients and the publish wish and need to hear, with the awareness and ability of clinicians to deliver these messages. There are clearly misconceptions and uncertainties that need to be addressed when engaging directly with patients and the public and in preparing supporting educational material.

Cell and gene therapies offer huge potential and equally large challenges to health systems and wider society. To capitalise on the benefits and address the challenges, it is essential to have the engagement of patient and the public, built into all stages of the development, introduction and review of use of these therapies. There is interesting work done to date and much to build on, but education and engagement is really only beginning and much more needs to be done as the roll out of novel therapies escalates.

Summary points

- The development and introduction of novel cell and gene therapies presents complex social, ethical and economic challenges for health systems .
- It is important that patients and the public are aware of, and understand the issues involved, and can contribute to debate on these issues.

- This scoping review was undertaken to map out the current understanding of patient and public perspectives on these topics, and thus inform the need for future research, education and awareness raising activities.
- It found that there is a body of literature available for study, but little of this is recently published, it is often of uncertain or limited methodological quality, and it spans a wide variety of cultural and socio-political contexts.
- The identified evidence focuses upon therapies in research or hypothetical therapies. No published literature was identified which considered perspectives of patients receiving currently licensed therapies.
- Levels of knowledge among patients and the public were extremely variable. A disconnect was seen between patients' and the publics' expectations of therapies and the scientific and clinical reality.
- Acceptance of the therapies appeared generally strong.
- There is a need for tailored education activities, which address misconceptions. Qualitative research examining perspectives in relation to the current and forthcoming therapies is also required.

References

1. REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf
2. DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1410944582971&uri=CELEX:02001L0083-20121116
3. Zheng XH, Zhang XY, Dong QQ, Chen F, Yang SB, Li WB. Efficacy and safety of chimeric antigen receptor-T cells in the treatment of B cell lymphoma: a systematic review and meta-analysis. *Chin Med J (Engl)* 133(1), 74-85 (2020).
4. Muller P, Lemcke H, David R. Stem Cell Therapy in Heart Diseases - Cell Types, Mechanisms and Improvement Strategies. *Cell Physiol Biochem* 48(6), 2607-2655 (2018).
5. Dothel G, Raschi E, Rimondini R, De Ponti F. Mesenchymal stromal cell-based therapy: Regulatory and translational aspects in gastroenterology. *World J Gastroenterol* 22(41), 9057-9068 (2016).
6. Alessandrini M, Preynat-Seauve O, De Bruin K, Pepper MS. Stem cell therapy for neurological disorders. *S Afr Med J* 109(8b), 70-77 (2019).
7. Ziccardi L, Cordeddu V, Gaddini L *et al*. Gene Therapy in Retinal Dystrophies. *Int J Mol Sci* 20(22), (2019).
8. Elverum K, Whitman M. Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine. *Gene Ther* doi:10.1038/s41434-019-0074-7 (2019).
9. Munn Z, Peters MDJ, Stern C, Tufanaru C, Mcarthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol* 18(1), 143 (2018).
10. Lloyd-Williams H, Hughes DA. A systematic review of economic evaluations of advanced therapy medicinal products. *Br J Clin Pharmacol* doi:10.1111/bcp.14275 (2020).
11. Liberati A, Altman DG, Tetzlaff J *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 339 b2700 (2009).
12. Kim YS, Chung DI, Choi H *et al*. Fantasies about stem cell therapy in chronic ischemic stroke patients. *Stem Cells Dev* 22(1), 31-36 (2013).
13. Aked J, Delavaran H, Lindvall O, Norrving B, Kokaia Z, Lindgren A. Attitudes to Stem Cell Therapy among Ischemic Stroke Survivors in the Lund Stroke Recovery Study. *Stem Cells and Development* 26(8), 566-572 (2017).
14. Jacob KJ, Kwon BK, Lo C, Snyder J, Illes J. Perspectives on strategies and challenges in the conversation about stem cells for spinal cord injury. *Spinal Cord* 53(11), 811-815 (2015).
15. Nelles M, Stieger K, Preising MN, Kruse J, Lorenz B. Shared decision-making, control preferences and psychological well-being in patients with RPE65 deficiency awaiting experimental gene therapy. *Ophthalmic Res* 54(2), 96-102 (2015).
16. Strong H, Mitchell M, Goldstein-Leever A *et al*. Patient Perspectives on Gene Transfer Therapy for Sickle Cell Disease. [Erratum appears in Adv Ther. 2017 Aug 2;:; PMID: 28770518]. *Advances in Therapy* 34(8), 2007-2021 (2017).
17. Wright B, Emmanuel A, Athanasakos E *et al*. Women's views on autologous cell-based therapy for post-obstetric incontinence. *Regenerative Medicine* 11(2), 169-180 (2016).
18. Jannetta EE, Cochrane SC, Morris PG, Dewar MH, Innes JA. A qualitative study of cystic fibrosis (CF) patients' expectations of gene therapy. *Journal of Cystic Fibrosis* 1) S101 (2010).
19. Hodges RJ, Bardien N, Wallace E. Acceptability of stem cell therapy by pregnant women. *Birth (Berkeley, Calif.)* 39(2), 91-97 (2012).
20. Clover AJ, O'neill BL, Kumar AH. Analysis of attitudes toward the source of progenitor cells in tissue-engineered products for use in burns compared with other disease states. *Wound Repair & Regeneration* 20(3), 311-316 (2012).
21. King WD, Wyatt GE, Liu H, Williams JK, Dinardo AD, Mitsuyasu RT. Pilot assessment of HIV gene therapy-hematopoietic stem cell clinical trial acceptability among minority patients and their advisors. *Journal of the National Medical Association* 102(12), 1123-1128 (2010).

22. Nelissen S, Van Den Bulck J, Lemal M, Beullens K. Stem cell research: the role of information seeking and scanning. *Health Info Libr J* 33(4), 269-282 (2016).
23. Cunningham NA, Abhyankar P, Cowie J, Galinsky J, Methven K. Regenerative medicine: Stroke survivor and carer views and motivations towards a proposed stem cell clinical trial using placebo neurosurgery. *Health Expect* 21(1), 367-378 (2018).
24. Peay H, Fischer R, Beaverson K *et al*. Parent and adult patient attitudes about gene therapy as a therapeutic option for duchenne muscular dystrophy. *Value in Health* 21 (Supplement 1) S256 (2018).
25. Eijkholt M, Kwon BK, Mizgalewicz A, Illes J. Decision-making in stem cell trials for spinal cord injury: the role of networks and peers. *Regenerative Medicine* 7(4), 513-522 (2012).
26. Chung SJ, Koh SB, Ju Y-S, Kim JW. Nationwide Survey of Patient Knowledge and Attitudes towards Human Experimentation Using Stem Cells or Bee Venom Acupuncture for Parkinson's Disease. *JMD* 7(2), 84-91 (2014).
27. Einsiedel E, Premji S, Geransar R, Orton NC, Thavaratnam T, Bennett LK. Diversity in public views toward stem cell sources and policies. *Stem cell rev* 5(2), 102-107 (2009).
28. Benjaminy S, Macdonald I, Bubela T. "Is a cure in my sight?" Multi-stakeholder perspectives on phase I choroideremia gene transfer clinical trials. *Genetics in Medicine* 16(5), 379-385 (2014).
29. Tanner C, Petersen A, Munsie M. 'No one here's helping me, what do you do?': Addressing patient need for support and advice about stem cell treatments. *Regenerative Medicine* 12(7), 791-801 (2017).
30. Allum N, Allansdottir A, Gaskell G *et al*. Religion and the public ethics of stem-cell research: Attitudes in Europe, Canada and the United States. *PLoS ONE* 12 (4) (no pagination)(e0176274), (2017).
31. Dasgupta I, Bollinger J, Mathews DJ, Neumann NM, Rattani A, Sugarman J. Patients' attitudes toward the donation of biological materials for the derivation of induced pluripotent stem cells. *Cell Stem Cell* 14(1), 9-12 (2014).
32. King E, Lyall C. What's in a name: are cultured red blood cells 'natural'? *Sociol Health Illn* 40(4), 687-701 (2018).
33. Nisbet MC, Becker AB. Public opinion about stem cell research, 2002 to 2010. *Public Opinion Quarterly* 78(4), 1003-1022 (2014).
34. Rachul C, Caulfield T. Gordie Howe's Stem Cell 'Miracle': A Qualitative Analysis of News Coverage and Readers' Comments in Newspapers and Sports Websites. *Stem Cell Reviews and Reports* 11(5), 667-675 (2015).
35. Robillard JM, Roskams-Edris D, Kuzeljevic B, Illes J. Prevailing public perceptions of the ethics of gene therapy. *Human Gene Therapy* 25(8), 740-746 (2014).
36. Robillard JM, Whiteley L, Johnson TW, Lim J, Wasserman WW, Illes J. Utilizing social media to study information-seeking and ethical issues in gene therapy. *Journal of medical Internet research* 15(3), e44 (2013).
37. Sipp D. Identity and ownership issues in the regulation of autologous cells. *Regenerative Medicine* 12(7), 827-838 (2017).
38. Stewart CJ, Miller C, Mcpherson C *et al*. Patient's attitude towards the donation and use of adipose tissue and adipose derived stem cells for research. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 68(4), 588-589 (2015).
39. Hudson J, Orviska M. European attitudes to gene therapy and pharmacogenetics. *Drug Discov Today* 16(19-20), 843-847 (2011).
40. Evans MD, Kelley J. US attitudes toward human embryonic stem cell research. *Nat biotechnol* 29(6), 484-488 (2011).
41. Blendon RJ, Gorski MT, Benson JM. The Public and the Gene-Editing Revolution. *N Engl J Med* 374(15), 1406-1411 (2016).
42. Wang JH, Wang R, Lee JH *et al*. Public Attitudes toward Gene Therapy in China. *Mol Ther Methods Clin Dev* 6 40-42 (2017).
43. Shineha R, Inoue Y, Ikka T, Kishimoto A, Yashiro Y. A Comparative Analysis of Attitudes on Communication Toward Stem Cell Research and Regenerative Medicine Between the Public and the Scientific Community. *Stem Cells Transl Med* 7(2), 251-257 (2018).

44. Horch JD, Carr ECJ, Harasym P, Burnett L, Biernaskie J, Gabriel V. Firefighter willingness to participate in a stem cell clinical trial for burns: A mixed methods study. *Burns* 42(8), 1740-1750 (2016).
45. Bubela T, Li MD, Hafez M, Bieber M, Atkins H. Is belief larger than fact: expectations, optimism and reality for translational stem cell research. *BMC Med* 10 133 (2012).
46. Vicsek L, Gergely J. Media presentation and public understanding of stem cells and stem cell research in Hungary. *New Genetics and Society* 30(1), 1-26 (2011).
47. Blendon RJ, Kim MK, Benson JM. The public, political parties, and stem-cell research. *New England Journal of Medicine* 365(20), 1853-1856 (2011).
48. Ryan, Scott, Reeves *et al*. Eliciting public preferences for healthcare: a systematic review of techniques. *Health Technol Assess* 5 (2001).
49. Bourke SM, Plumpton CO, Hughes DA. Societal Preferences for Funding Orphan Drugs in the United Kingdom: An Application of Person Trade-Off and Discrete Choice Experiment Methods. *Value Health* 21(5), 538-546 (2018).

Reference annotations

1. Munn Z, Peters MDJ, Stern C, Tufanaru C, Mcarthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol* 18(1), 143 (2018).*

   A helpful clarifcation of the differences between systematic and scoping review approaches and the role of each of these.

2. Blendon RJ, Gorski MT, Benson JM. The Public and the Gene-Editing Revolution. *N Engl J Med* 374(15), 1406-1411 (2016).*

   A good introductory discussion on public views around the use of gene therapy.

3. Elverum K, Whitman M. Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine. *Gene Ther* doi:10.1038/s41434-019-0074-7 (2019).**

   Provides a helpful introduction on the topic of cell and gene therapies and some of them challenges for enabling patients to benefit from these.

Legend of Figures and Tables

Figure 1 PRISMA diagram showing literature search and selection process

Table 1: PICO characteristics

Table 2: Participants

Table 3: Type of therapy

Table 4: Study setting

Table 5: Methods of data collection

Table 6: summary of key findings

Table 7: Included studies

α18

Appendix 1

Literature search

Searches were conducted between 4th December 2018 and 5th April 2019, using the sources listed below. The search was restricted to studies published from the 1st January 2009 onwards.

- Medline
- Embase
- CINAHL
- PsychINFO
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- DARE
- HTA database
- Current Controlled Trials
- Prospero database

The following shows the final search strategy used to search Medline. The strategy was adapted to search the other databases. All search strategies are available on request.

Medline	
ATMP Stem	
1	exp "Cell- and Tissue-Based Therapy"/
2	exp Genetic Therapy/
3	Regenerative Medicine/
4	Tissue Engineering/
5	exp Gene Transfer Techniques/
6	exp stem cells/
7	exp Multipotent Stem Cells/
8	Induced Pluripotent Stem Cells/
9	exp Stromal Cells/
10	stem cell research/
11	(advanced therapy medicinal product$ or advanced therapy medicinal product$ or atmp$).tw.
12	regenerative medicine$.tw.
13	advanced therap$.tw.
14	(gene-therapy medicinal product$ or gene therapy medicinal product$ or gtmp$).tw.
15	(cell-therapy medicinal product$ or cell therapy medicinal product$ or ctmp$).tw.
16	(tissue engineered product$ or tissue-engineered product$ or tep or teps).tw.
17	(regenerative medicine advanced therap$ or rmat$).tw.
18	"human cells, tissues, and cellular and tissue-based products (HCT/Ps)".tw.
19	"human cells, tissues, and cellular and tissue-based product (HCT/P)".tw.
20	regenerative therap$.tw.
21	("cell and gene therapy product" or "cell and gene therapy products" or cgtp or cgtps).tw.
22	or/1-21
23	(Tisagenlecleucel or Kymriah or cart 19 or cart19 or "ctl 019" or ctl019).tw.
24	(Axicabtagene ciloleucel or Yescarta or kte c19 or ktec19).tw.
25	(Voretigene neparvovec-rzyl or Voretigene neparvovec?rzyl or Luxturna).tw.
26	(Talimogene laherparepvec or Imlygic or oncovex or t vec).tw.
27	(Strimvelis or gsk 2696273 or gsk2696273).tw.
28	Holoclar.tw.
29	MACI.tw.
30	(Provenge or sipuleucel t or apc 8015 or apc8015).tw.

31	(Glybera or alipogene tiparvovec or "amt 011" or amt011 or aav1 lpls447x).tw.
32	Zalmoxis.tw.
33	Spherox.tw.
34	or/23-33
35	22 or 34
Patient Filter (adapted SIGN Patient Issues filter)	
36	((patient$ or consumer$ or public) adj2 (decisi$ or decid$)).ti,ab.
37	"Patient Acceptance of Health Care"/
38	exp attitude to health/
39	Patient Preference/
40	"patient satisfaction".ti.
41	exp health education/
42	patient education as topic/
43	health knowledge, attitudes, practice/
44	"informed choice".ti,ab.
45	"shared decision making".ti,ab.
46	("focus group" adj3 (patient$ or parent$ or famil$ or spouse$ or public)).ti,ab.
47	Consumer Advocacy/
48	patient advocacy/
49	exp professional-patient relations/
50	((patient$ or consumer$ or parent$ or famil$ or spouse$ or carer$ or public) adj (attitude$ or involvement or desir$ or perspective$ or activation or view$ or preference$ or experience$ or knowledge$ or understand$ or awareness$)).ti,ab.
51	exp decision making/
52	exp communication/
53	vignette*.ti,ab.
54	"focus group$".ti,ab.
55	focus groups/
56	exp empirical research/
57	narration/
58	(meta-ethnography or metaethnography).ti,ab.
59	grounded theor*.ti,ab.
60	hermeneutic.ti,ab.
61	(inductive adj2 (analys* or grounded or reasoning)).ti,ab.
62	(ethnograph* or ethnological or ethnomethodol* or ethnonursing research).ti,ab.
63	qualitative.ti.
64	exp qualitative research/
65	(qualitative adj (research or stud* or data)).ab.
66	exp Community Participation/
67	Public Opinion/
68	or/36-67
69	35 and 68
70	limit 69 to yr="2009 -Current"

Figure 1 PRISMA diagram showing literature search and selection process[11]

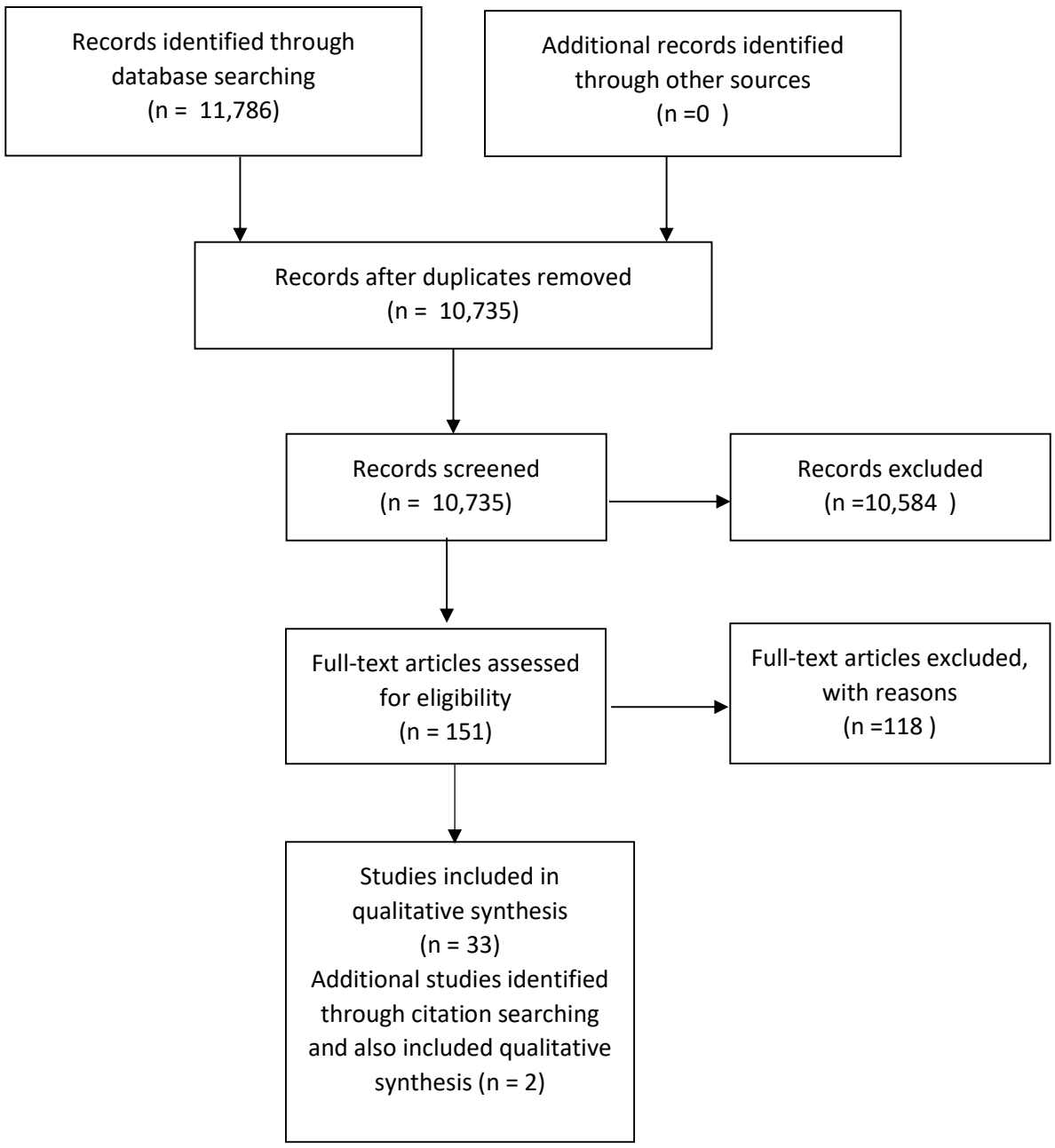

Table 7: Included studies

Full data extraction tables for the included studies are available from the authors on request.

Author	Type of therapy	Participants	Indication	Country	Time of data collection	Design/method
Aked et al. (2017)	Cell	Patients	Ischaemic stroke	Sweden	Between 2014 and 2017	Quantitative questionnaire
Allum et al. (2017)	Cell	Public	General	Europe; USA; Canada	2005	Quantitative questionnaire
Benjaminy et al. (2014)	Gene	Patients; clinicians; patient advocates	Choroideremia	Canada	June 2011 to June 2012	Semi-structured interviews
Blendon et al. (2016)	Gene	Public	General	US	1986 to 2016	Analysis of public opinion polls
Bubela et al. (2012)	Cell	Media (newspaper articles)	General	Canada	1990 to 2010	Word frequency analysis
Chung et al. (2014)	Cell	Patients; carers	Parkinson's disease	Korea	April 2013 to June 2013	Questionnaire
Clover et al. (2012)	Cell/tissue engineering	Patients	Burns	Ireland	2010	Quantitative questionnaire
Cunningham et al. (2018)	Cell	Patients; carers	Stroke	UK	June to October 2016	Focus group (conversation café)
Dasgupta et al. (2014)	Cell	Public	General	USA	2014 or earlier	Focus group
Eijkholt et al. (2012)	Cell	Friends and family; patients	Spinal cord injury	Canada	June 2009 to February 2010	Focus groups and interviews
Einsiedel et al. (2009)	Cell	Patients; public; caregivers	General	Canada	2009 or earlier - not specified	Focus groups
Evans and Kelley (2011)	Cell	Public	General	USA	2009	Quantitative questionnaire
Hodges et al. (2012)	Cell	Patients (pregnant women)	General and 15 specific disorders	Australia	2009/2010	Quantitative questionnaire
Horch et al. (2016)	Cell	Public (firefighters)	Burns	Canada	2016 or earlier	Mixed methods; quantitative online survey followed by a qualitative

						semi-structured interview
Hudson and Orviska (2011)	Gene	Public	General	Europe	2005	Eurobarometer public opinion survey
Jacob et al. (2015)	Cell	Patients	Spinal cord injury	Canada; USA	2015 or earlier	Qualitative interviews
Jannetta et al. (2010)	Gene	Patients	Cystic fibrosis	UK	2009 or earlier - not specified	Qualitative interviews
Kim et al. (2013)	Cell	Patients	Ischaemic stroke	South Korea	Jan to May 2011	Quantitative and qualitative interviews
King et al. (2010)	Cell	Patient; Public	HIV/AIDs	USA	2010 or earlier	Focus groups
King and Lyall (2018)	Cell	Public	Blood transfusion	Scotland	2011 to 2017	Ethnographic study; 15 interviews and 12 focus groups
Nelissen et al. (2016)	Cell	Patients; public	Cancer	Belgium	2016 or earlier	Cross sectional survey
Nelles et al. (2015)	Gene	Patients	Genetic eye disease	Germany	2015 or earlier	Quantitative questionnaires and qualitative interviews
Nisbet et al. (2014)	Cell	Public	General	USA	2002 to 2010	Quantitative surveys
Peay et al. (2018)	Gene	Patients; carers	Duchenne Muscular Dystrophy	USA	March to May 2017	Qualitative interviews
Rachul and Caulfield (2015)	Cell	Public	General	USA; Canada	Earlier than February 2015	Qualitative analysis of news media articles and readers' comments
Robillard et al. (2013)	Gene	Public	General	Canada	2006-2010	Content analysis
Robillard et al. (2014)	Gene	Public	General	USA; Canada	2014 or earlier	Online survey
Shineha et al. (2018)	Cell	Public; scientists	General	Japan	October 2015 to March 2016	Quantitative questionnaire
Sipp D. (2017)	Cell	Public	General	USA	2016	Content analysis
Stewart et al. (2015)	Cell	Public	General	UK	Aug to Sep 2014	Qualitative interviews and questionnaire
Strong H et al. (2017)	Gene	Patients	Sickle cell	USA	2010-2012	Focus groups
Tanner et al. (2017)	Cell	Patients; carers; clinicians;	General	Australia	2012-2014	Qualitative interviews

		patient advocates				
Vicsek and Gergely (2011)	Cell	Media newspaper articles; public	General	Hungary	2006 to 2008	Qualitative content analysis and focus groups
Wang et al. (2017)	Gene	Public; clinicians	General	China	August 2016 to November 2016	Online survey
Wright et al. (2016)	Cell	Patients	Post-obstetric incontinence	UK	2016 or earlier	Quantitative questionnaire with some free text response options

Disclosures

Funding statement

This work was funded by a Midlands-Wales Advanced Therapies Treatment Centre (MW-ATTC) programme grant from Innovate UK to a consortium of partners including Health Technology Wales, the Welsh Blood Service and the University of Birmingham. The funder was not involved in any aspect of the research work.

Competing Interests statement

O.L.A, P.N.N and M.J.C were supported by the National Institute of Health Research (NIHR) Birmingham Biomedical Research Centre (BRC), West Midlands, Birmingham. O.L.A also receives funding from the Health Foundation and personal fees from Gilead Sciences Ltd. M.J.C and P.N.N are NIHR Senior Investigators. M.J.C receives funding from the NIHR Applied Research Collaboration, West Midlands and the NIHR Surgical Reconstruction and Microbiology Research Centre at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK (part of UK Research and Innovation), Macmillan Cancer Support, UCB Pharma. M.J.C has received personal fees from Astellas, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK and the Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work. The remaining authors declare no competing interests. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, NHS or the Department of Health and Social Care.

Related publication

A shorter discursive piece related to this work has been accepted for publication in the Nature Communications Journal https://www.nature.com/ncomms/

This main paper outlines in full the methodology used, the results obtained and suggestions for further research required on this topic.