



Genetic counseling and testing practices for late-onset neurodegenerative disease: a systematic review

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Received: 9 December 2020 / Revised: 10 February 2021 / Accepted: 10 February 2021 / Published online: 1 March 2021
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Abstract

Objective To understand contemporary genetic counseling and testing practices for late-onset neurodegenerative diseases (LONDS), and identify whether practices address the internationally accepted goals of genetic counseling: interpretation, counseling, education, and support.

Methods Four databases were systematically searched for articles published from 2009 to 2020. Peer-reviewed research articles in English that reported research and clinical genetic counseling and testing practices for LONDS were included. A narrative synthesis was conducted to describe different practices and map genetic counseling activities to the goals. Risk of bias was assessed using the Quallsyst tool. The protocol was registered with PROSPERO (CRD42019121421).

Results Sixty-one studies from 68 papers were included. Most papers focused on predictive testing (58/68) and Huntington's disease (41/68). There was variation between papers in study design, study population, outcomes, interventions, and settings. Although there were commonalities, novel and inconsistent genetic counseling practices were identified. Eighteen papers addressed all four goals of genetic counseling.

Conclusion Contemporary genetic counseling and testing practices for LONDS are varied and informed by regional differences and the presence of different health providers. A flexible, multidisciplinary, client- and family-centered care continues to emerge. As genetic testing becomes a routine part of care for patients (and their relatives), health providers must balance their limited time and resources with ensuring clients are safely and effectively counseled, and all four genetic counseling goals are addressed. Areas of further research include diagnostic and reproductive genetic counseling/testing practices, evaluations of novel approaches to care, and the role and use of different health providers in practice.

Keywords Genetic counseling · Genetic testing · Neurodegenerative disease · Huntington's disease · Pre-symptomatic testing

Introduction

Patients with late-onset neurodegenerative diseases (LONDS, Box 1), and their at-risk relatives, face complex and challenging decisions when considering genetic testing [1]. Genetic

testing, through next-generation sequencing, is becoming more common in neurology clinics and allows multiple LOND genes to be screened concurrently at a lower cost and greater speed than ever before [2]. Genetic counseling facilitates and supports individuals through the process of decision-making

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about testing [1]. Adequate knowledge and time allocated to provide genetic counseling are vital to maximize the health benefits of genetic testing while minimising harm to the client and their relatives [1, 3].

According to the Human Genetics Society of Australasia and the National Society of Genetic Counselors of the United States of America (USA), the activities of genetic counseling should integrate the following four goals:

1. Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence [4, 5].
2. Education about the natural history of the condition, inheritance pattern, testing, management, prevention, support resources, and research [4, 5].
3. Counseling to promote informed choices in view of risk assessment, family goals, ethical and religious values [4–6].
4. Support to encourage the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder [4, 6].

Genetic counselors are allied health professionals trained to provide this specialized care, however, the international shortage of genetic counselors requires other health providers to assume the role [7]. Health providers from outside of the specialty of genetics are often unprepared to integrate genetic and genomic health information into routine clinical care due to a lack of resources and guidelines, low confidence in initiating genetics discussions, and concerns about discrimination and psychological harm [8]. Guidelines and protocols for diagnostic, predictive, and reproductive genetic testing and associated counseling have been developed for a range of LONs [9–15] and are informed by the Huntington's disease (HD) guidelines [9, 10, 16, 17]. However, guidelines are not always translated into practice [18, 19]. Examining contemporary genetic counseling practices for individuals undergoing diagnostic, predictive, and reproductive testing for LONs is therefore important to understand whether these practices adequately address all four genetic counseling goals.

The primary aim of this review was to establish a comprehensive understanding of contemporary genetic counseling and testing practices for LONs. The secondary aim was to identify the extent to which current practices address the established goals of genetic counseling. The findings will inform the development of updated genetic counseling and testing models of service delivery for LONs and highlight future research priorities.

Box 1 Definitions of key terms used in systematic review

Genetic counseling: a communication process that aims to help individuals understand and adapt to the medical,

psychological, familial, and reproductive implications of the genetic contribution to specific health conditions

[4–6]. It integrates the four goals of (1) Interpretation of family and medical histories [4, 5], (2) Education about the condition [4, 5], (3) Counseling to promote informed choices, and (4) Support to encourage the best possible adjustment [4, 6]. The term 'genetic counseling' here encompasses genetic counseling without genetic testing and genetic counseling provided both pre-, during and post-testing.

Diagnostic genetic testing: the initial search for pathogenic variants (mutations), often performed to confirm a diagnosis in a patient with symptoms consistent with the disease/ genetic condition. When a pathogenic variant is identified through diagnostic testing, predictive or reproductive testing becomes available to biological relatives.

Predictive (or pre-symptomatic) testing: a test performed to confirm whether an asymptomatic relative has inherited a pathogenic variant previously identified in a relative, which implies a future risk of developing the disease.

Reproductive testing: a test performed to prevent inheritance of a pathogenic variant through testing a pregnancy (prenatal diagnosis, and subsequent termination of pregnancy if the variant is confirmed) or in vitro fertilisation (IVF, pre-implantation genetic diagnosis). Individuals who do not wish to know their status as a pathogenic variant carrier may be able to undergo reproductive testing through exclusion or non-disclosure testing [85].

Late-onset neurodegenerative diseases (LONs): for the purpose of this review, LONs included mostly adult-onset, highly penetrant, and autosomal dominantly inherited neurodegenerative conditions. This included (but was not limited to) Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, genetic prion diseases, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), muscular dystrophies, hereditary spastic paraplegias, spinocerebellar ataxias or neuropathies (including Charcot-Marie-Tooth disease and familial amyloid polyneuropathy). Each is expected to have similar potential psychological sequelae due to shared genetic and phenotypic characteristics. For example, all included LONs are considered progressive and can affect movement, cognition, behavior, personality, or communication [90, 91]. Although these LONs (generally) have few treatments or preventative options available to stop or slow progression, individuals may

use genetic testing results to plan their future, including undergoing reproductive testing. Genes associated with lower penetrance were excluded (e.g., APOE in Alzheimer's disease and all of the currently known Parkinson's disease genes), as were X-linked conditions (e.g., Duchenne or Becker muscular dystrophy, Kennedy's disease).

Methods

Protocol and registration

The systematic review protocol was registered on 01/20/2019 with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019121421). This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [20] (Online resource 1).

Eligibility criteria

The inclusion and exclusion criteria are listed in Table 1 and were developed using the PICOS framework [20]. Only papers in English were included due to time and cost constraints. To highlight current practices used since the advent of next-generation sequencing technology, only papers

published since 2009 were included. Additional key terms and justification for the eligibility criteria are outlined in Box 1. As we hoped to ascertain commonalities across the included LONDS, condition-specific aspects of genetic testing and counseling, such as anticipation in triplet repeat disorders or laboratory experiences, were not included.

Literature search strategy

Four electronic databases (CINAHL, MEDLINE, PsycINFO, and EMBASE) were searched using terms related to the target disease group, intervention, and publication dates (Online resource 2). Searches were combined and deduplicated using Endnote X9. Further references were elicited through backward-searching reference lists of included papers and forward-searching using Web of Science. The searches were re-run before the final analysis on 27 May 2020.

Study selection

The primary (AC) and secondary reviewer (ROS) piloted the inclusion criteria. AC then screened all references against the criteria at the title and abstract and full-text screening stage, and ROS independently assessed 10% of titles and abstracts and 20% of full texts. Any disagreements were resolved through discussion. Where no agreement was

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
<i>Population</i>	
Health providers of genetic testing and/or counseling for late-onset neurodegenerative diseases (LONDS), OR	Childhood-onset, lower penetrance, autosomal recessive or X-linked inherited diseases
Adults with or at risk of a LOND or medical guardians of adults with a LOND	Included population not easily stratified from excluded population (e.g. if there are multiple diseases or ages included)
<i>Intervention</i>	
Any aspect of genetic counseling practice, both before, during, or after genetic testing. This includes diagnostic testing, predictive or pre-symptomatic testing, and reproductive testing	Laboratory methods Research genetic testing where the result is never disclosed to the individual
<i>Comparator</i>	
No comparator	
<i>Outcomes</i>	
Key components and activities of the genetic testing or counseling process including the role and involvement of health providers	Outcomes not specific to the genetic counseling or testing process
Goals of genetic counseling or testing including experience, outcomes, and recommendations that inform practice (Goals include any of the four goals of genetic counseling: interpretation, education, counseling, support)	Likelihood of detecting a pathogenic variant, population frequencies, phenotypic data, uptake rate of testing, and family communication, without any information on clinical genetic testing or counseling practices
<i>Study design and context</i>	
Any method of peer-reviewed research, published after 1 January 2009, in English, from worldwide	Non-peer-reviewed papers, editorials, grey literature, non-systematic reviews, book chapters or dissertations Practice recommendation or guideline papers that do not explicitly stem from research or clinical experience

reached, the decision to include or exclude was made by a third reviewer (AM). Inter-rater reliability after title and abstract and full-text screening, respectively, demonstrated a level of agreement of 96.8% and 91.5%, and at least strong agreement using the prevalence-adjusted bias-adjusted kappa (PABAK = 0.94 and 0.83) [21, 22]. The study selection process and reasons for exclusion are summarized in Fig. 1.

Data extraction and quality assessment

AC completed data extraction and critical appraisal forms for each included paper, then ROS verified and validated these. Data items were related to the research question (e.g. genetic testing type, health provider role and involvement, number of appointments, requirement of a support person, and activities involved) (Online resource 3). The activities involved in genetic counseling practice were extracted, grouped in key topic areas, and mapped against the four goals of genetic counseling [4–6].

The Quallsyst tool [23] was used to critically appraise the quality of included studies, as it allows for the assessment of quantitative and qualitative research across a broad range of study designs.

Narrative synthesis

A systematic narrative synthesis was performed to describe the variation between practices and activities [24]. A

meta-analysis was not possible due to the heterogeneity of included studies. No papers were excluded based on a quality threshold, but the methodological quality and potential biases between and within studies were assessed.

Results

Study characteristics and quality appraisal

Sixty-eight papers representing 61 studies were included (Table 2; Online resource 3). Several studies focused on more than one condition, testing or study type. The most commonly studied condition was Huntington's disease (HD) (41/68), and the majority of papers focused on predictive testing (58/68) and used qualitative methods (24/68). There were no randomized control trials. The total number of included participants is not easily comparable between studies given the variability in study design, study population, outcomes, interventions, and settings. Sixty papers (60/68) achieved a Quallsyst score of 0.80 or higher, indicating sound methodological quality for their study type.

Narrative synthesis: genetic counseling practices for LONDs

Findings from the narrative synthesis are summarized under the following topics: the involvement and role of health

Fig. 1 Summary of the study selection process, as recommended by PRISMA [20]

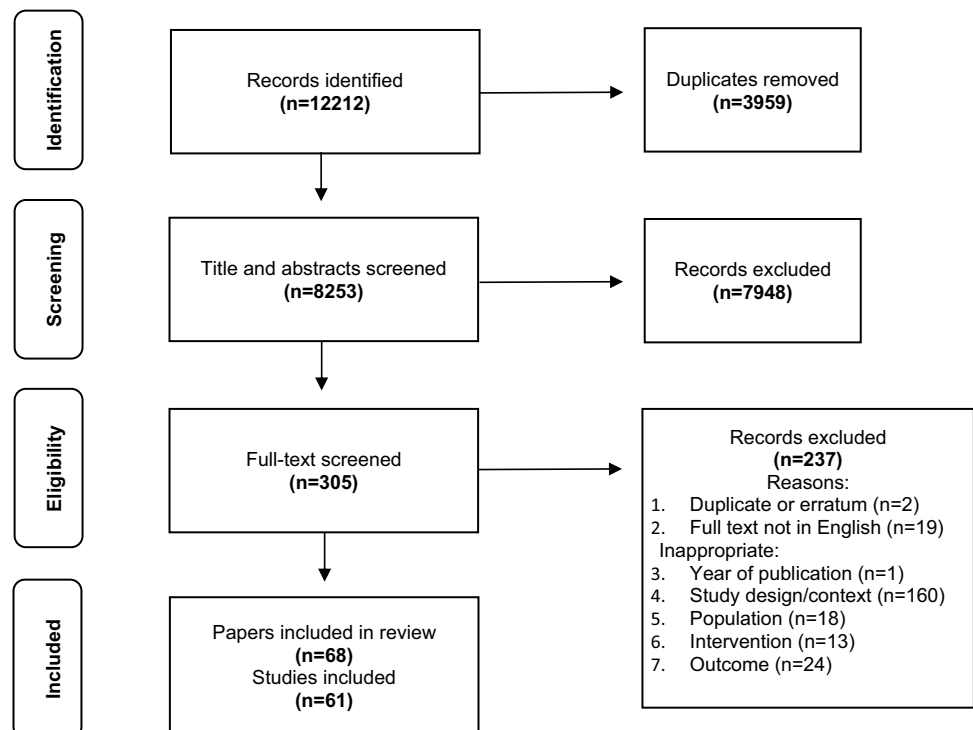


Table 2 Summary of included papers

Characteristics	Number of papers	Number of studies	References
<i>Conditions investigated^{a,b}</i>			
Huntington's disease (HD)	41	36	[25, 26, 28-37, 40-43, 46, 47, 49-51, 53, 55, 56, 58-61, 64-68, 70, 73, 92-97]
Spinocerebellar ataxias (SCAs- all subtypes)	12	10	[30, 33, 38, 39, 42-45, 53, 57, 96, 98]
Amyotrophic lateral sclerosis/Frontotemporal dementia (ALS/FTD)	11	10	[52, 55, 59, 63, 71, 72, 74, 75, 82, 99, 100]
Familial amyloid polyneuropathy (TTR-FAP)	7	6	[33, 35, 42, 43, 50, 53, 96]
Unspecified disease type or included >6 LONDS	5	5	[48, 76, 89, 101, 102]
Alzheimer's disease (AD)	3	3	[62, 69, 103]
Prion disease	2	2	[54, 104]
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	2	2	[27, 33]
Facioscapulohumeral muscular dystrophy (FSHD)	1	1	[105]
<i>Intervention type^b</i>			
Diagnostic genetic testing	17	17	[25, 37, 54, 59, 61, 62, 68, 70, 72, 74, 75, 93, 99-101, 103, 105]
Predictive genetic testing	58	51	[25-28, 30-33, 35-50, 52-57, 59-71, 73, 74, 76, 89, 92-97, 99, 100, 102, 104, 105]
Reproductive genetic testing	11	11	[29, 39, 41, 51, 57, 58, 76, 82, 94, 98, 100]
Unspecified genetic testing type	1	1	[34]
<i>Main author location(s)^b</i>			
Europe	33	29	[26-28, 30-33, 35, 38, 42, 44, 46, 48-51, 53, 56, 58, 60, 61, 63-66, 74, 75, 89, 94, 96, 99, 101, 104]
North America	29	26	[25, 29, 34, 36, 37, 39-41, 45, 47, 52, 54, 55, 57, 59, 62, 68-73, 82, 92, 93, 95, 97, 98, 103]
South America	2	2	[43, 44]
Asia	2	2	[102, 105]
Africa	1	1	[67]
Australia	2	2	[76, 100]
<i>Source of genetic counseling practice</i>			
Practice sourced from clinical experience	32	31	[27, 29, 33, 38, 39, 41, 44-46, 49, 54-59, 62, 63, 67, 68, 70, 72, 74-76, 94, 97, 99-102, 105]
Practice trialed in clinical setting	6	4	[30, 34, 40, 64-66]
Practice recommended from clinical research	20	16	[26, 28, 31, 32, 35, 36, 42, 43, 50-53, 60, 71, 89, 92, 95, 96, 103, 104]
Practice recommended from non-clinical research	10	10	[25, 37, 47, 48, 61, 69, 73, 82, 93, 98]
<i>Study type^b</i>			
Qualitative	24	19	[25, 26, 28, 36, 37, 42, 47, 51, 53, 56, 60, 61, 64-66, 69, 71, 73, 82, 89, 92, 93, 96, 104]
Case series	21	20	[27, 30, 39, 41, 43-45, 49, 52, 55-57, 63, 67, 70, 94, 96, 101, 103-105]
Cohort study	14	14	[27, 31, 33-36, 38, 40, 43, 46, 50, 58, 60, 95]
Case study	11	11	[44, 54, 59, 62, 63, 68, 74-76, 100, 105]
Cross-sectional survey	9	9	[29, 32, 69, 72, 73, 97-99, 102]
Delphi survey	1	1	[48]
Before and after study	1	1	[64]
<i>Risk of Bias assessment</i>			
>0.90	50	46	[25-35, 37-45, 48, 50, 51, 53-55, 57-59, 61, 64-66, 68, 70, 72, 74-76, 89, 93-100, 102, 105]
0.80-0.89	10	10	[36, 46, 60, 62, 67, 69, 71, 73, 82, 101]
0.70-0.79	5	5	[47, 49, 52, 92, 103]
0.60-0.69	1	1	[56]
0.50-0.59	2	2	[63, 104]

^aOnly data on conditions of interest extracted

^bSome papers included multiple categories

providers, the testing protocol, barriers to accessing genetic counseling and testing, activities involved in genetic counseling practice, and addressing the goals of genetic counseling. Most of the results relate to predictive testing, but diagnostic and reproductive testing practices are reported where available.

(i) *The involvement and role of health providers*

A multidisciplinary team of two or more health providers was involved in the genetic counseling practice in 33 papers (Table 3). The specific role of each health provider within the team was not always clearly described, but 29 papers mentioned the role of neurologists, psychiatrists, and psychologists in assessing symptoms of disease or risk factors for coping. Five studies highlighted the need for increased training for those working in primary care [25–27], psychiatry [28, 29], and neurology [29]. The value of having certain providers in the team was formally evaluated in three studies [30–32]. In one study, most clients were satisfied with their neurologist appointment, particularly those who consulted a neurologist before, compared to after, receiving predictive testing results [32]. Although instruments to assess anxiety, depression, and other psychopathology informed risk of post-test distress [33–35], formal psychiatric testing provided more information than a questionnaire in one study [31]. In one practice trialed in a clinical setting, a psychologist or psychiatrist was involved in a clinical case conference where they never met the client but discussed the case in detail before testing and results disclosure [30]. This supported both the client and clinician throughout the predictive testing process [30].

(ii) *The testing protocol*

Up to four pre-testing appointments were required in some predictive testing protocols (Table 3). After testing, two studies recommended offering additional appointments to provide further education about the condition and discuss risk perception and beliefs [36, 37]. Sixteen studies encouraged the client to attend short or longer-term psychological follow-up sessions, either if a pathogenic variant was confirmed [26, 28, 38], regardless of the result [27, 30, 33, 39–48], or if requested or required based on pre-test discussions [46, 49, 50]. Acceptance of follow-up varied, with up to 80% of participants choosing to proceed with post-test psychological follow-up in two studies on predictive testing [38, 49], and none proceeding in two other studies in predictive [43] and reproductive testing [51].

In some practices, clients were required to complete structured psychological or psychosocial surveys [30, 31, 33–35, 40, 43–45, 50, 52], or disease-specific neurological or objective knowledge measurement tools

[30, 53] in addition to, or instead of, a formal neurological or psychiatric/psychological assessment (Table 3). Health providers recommended deferring testing in some studies if high risk of future clinical distress [31, 33, 35, 41, 43, 45, 46, 52, 54], problematic motivation [31, 49, 54–56], or the absence of a support system [31, 52, 54] were identified. One case series highlighted three situations where individuals still underwent predictive testing despite having high-risk psychopathology [55]. The testing process included close interaction with the clients' psychiatric care team, and the outcome was successful in two of three cases [55]. Where symptoms were identified as part of the neurological or psychiatric/psychological assessment, the response varied. Many teams proceeded with predictive testing if clients perceived themselves as asymptomatic [28, 30, 41, 43, 44, 46, 57], while others excluded symptomatic individuals from their predictive testing protocol [45, 57]. In the one study that discussed neurological and psychological assessments in reproductive testing, a couple's request for IVF could be rejected if symptoms were present in a parent and the couple seemed unable to provide a stable home environment [58].

Variations regarding the requirement of a support person throughout the testing process were reported in 14 papers (Table 3). Some papers cautioned that the support person might require attention, support, or information, particularly if their first attendance is at the client's results appointment [25, 26, 28, 41, 51, 54]. One study suggested that support should not be sought from a relative who is having predictive testing concurrently, as this could create further anxiety [42]. A support person may also adopt the decision-making role, as described by one case study of a patient with ALS and a family history of HD, whose wife was given decision-making capacity regarding HD predictive testing given his terminal condition [59]. No included studies formally evaluated the effect of having a support person (or not).

In two studies, clients provided positive feedback about the counseling, support, and information received throughout the structured protocol [33, 46]. However, negative feedback was provided in nine studies [27, 33, 41–43, 46, 47, 53, 60]. Some clients were deterred by the length, complexity, rigidity, or content of the protocol (including total duration and number of consultations, and whether a support person was mandatory) [27, 33, 41–43, 46, 47, 53, 60], particularly if they had already decided to proceed with testing [53, 60]. Others were concerned that the psychological assessments pre-testing were unnecessary or that testing would be withheld based on the clients' psychological state [33, 41, 43, 47]. Consequently, fourteen papers suggested

Table 3 Variations among genetic counseling and testing practices for LONDS

Aspects of genetic counseling practice	Number of papers	References for each testing type		
		Diagnostic testing	Predictive testing	Reproductive testing
<i>Health providers involved in the testing team</i>				
Neurologist	24	[70, 72, 75, 101, 105]	[27, 30, 32, 38, 39, 42, 44–46, 49, 52, 55, 57, 59, 60, 67, 70, 71, 75, 95, 102, 105]	[39]
Geneticist	23	[75, 101, 105]	[27, 30, 32, 39, 41, 43–46, 48, 49, 52, 56, 60, 63, 67, 71, 102, 104, 105]	[39, 58]
Psychologist	21	[75, 101]	[27, 30, 38–41, 43–46, 48, 49, 56, 57, 60, 63, 67, 102, 104]	[39]
Genetic counselor	15	[70, 72, 105]	[39–41, 44, 45, 48, 52, 55, 57, 59, 70, 71, 102, 105]	[39]
Psychiatrist	7	[70]	[30, 31, 44, 49, 55, 70, 102]	
Nurse	7	[70, 72]	[48, 49, 56, 67, 70, 102]	
Social worker	6	[72]	[39, 44, 48, 49, 55]	[39]
Molecular biologist/ laboratory geneticist	3		[30, 48, 49]	
Family physician	2		[30, 57]	
Medical doctor (other or unspecified)	2		[39, 48]	[39]
Obstetrician/ gynaecologist	2			[41, 58]
Bioethicist	1		[39]	[39]
Neuropsychiatrist	1	[70]	[70]	
<i>Neurological assessment</i>				
Mandatory	11	[70]	[27, 30, 32, 33, 38, 39, 45, 46, 57, 70, 95]	
As needed	5		[41, 43, 44, 49]	[58]
Offered	1		[32]	
Where possible	2		[40, 47]	
<i>Psychiatric/ psychological assessments^a</i>				
Mandatory	16		[27, 30, 31, 38, 39, 41–43, 45, 55–57, 60, 63, 89, 104]	
As needed	9		[35, 41, 43, 44, 49, 52, 54, 71]	[58]
<i>Minimum recommended number of appointments</i>				
<i>Pretest</i>				
1	5	[105]	[52, 63, 71, 105]	[41]
1 + reflection time	3		[41, 49, 60]	
2	7		[30, 40, 42, 44, 46, 47, 56]	
3	4		[33, 41, 60, 67]	
4	4		[27, 38, 43, 44]	
<i>Post-test</i>				
1	17	[105]	[44, 52, 60, 63, 67, 71, 105]	
1 + follow-up encouraged	19		[26–28, 30, 33, 36–48]	[51]
<i>Support person at appointments^b</i>				
At results appointment	6			[27, 40, 42–44, 47]
Strongly encouraged	5	[59, 75]		[41, 42, 47]
Optional	3			[41, 43, 52]
Involvement of both members of a couple	3			[57, 58, 82]
Mandatory	1		[44]	

^aPsychological and psychiatric assessments have been combined as many studies were unclear about which health provider was involved^bA support person may be a family member or peer

predictive testing be conducted in a more individual, flexible way by adapting the protocol to the specific

needs, information processed and decision-making of the client [39, 40, 42, 44, 46–50, 57, 59, 61–63]. Adap-

tations included reducing the number of appointments [46, 48, 57, 59, 63], tailoring the content [46–48, 59, 63] or adapting the psychological support provided to each individual's needs [46, 50]. Still, no papers examined whether the number of pre- and post-test counseling sessions made a difference to outcomes. One UK series of studies trialed a new practice of support post-testing, with a novel standalone genetic counseling narrative group approach for individuals with a negative HD predictive test result [64] and a positive HD predictive test result [65, 66], as well as their partners [66]. The majority of participants were positive about the group session being a safe way to share experiences in a structured way [66], discuss difficult emotions, highlight coping resources, and feeling a sense of community [64, 65].

(iii) *Barriers to accessing genetic counseling and testing*

Ten studies described travel distance and time as barriers to accessing genetic counseling or testing [33, 42, 43, 47, 59, 62, 67–70] or adequate support throughout the process [47]. Geographical barriers were addressed by conducting telephone or telehealth sessions as part of a regular protocol or depending on client preference [40, 41, 52, 58, 71, 72]. In other studies, home visits [68] or satellite clinics [70] were conducted, a local health provider was upskilled so that remote testing and counseling would be available [40, 47], or multiple appointments were arranged on the same day for one client [67] or multiple relatives [62, 68]. No adverse effects of these modifications were reported, but only two studies evaluated these practices [40, 71].

Clients experienced difficulty accessing appropriate support or information in seven studies [44, 52, 62, 67–69, 73]. To address this barrier, educational materials were developed with the community in their preferred language [62, 67, 73], clients were given funding support to attend appointments [67], and the team met with local physicians to educate about genetic risk and health resources [62]. No studies evaluated the differences in access to or uptake of testing before and after implementing these new practices. One educational website was piloted with at-risk individuals, health providers, and other stakeholders, and positive feedback was received [73].

Eight studies noted different laws were present that may be a barrier to accessing genetic counseling and testing. This included discrimination based on genetic testing results [39, 52], access to termination of pregnancy for genetic disorders [44, 57], access to direct, exclusion or non-disclosure reproductive testing [58] and obligations to inform relatives about genetic results or family medical information (before or after death) [39, 49, 74, 75].

Client-specific barriers to accessing predictive or reproductive testing included the presence of an intervening at-risk relative [39, 41, 56, 76] or where there were identical twins [39]. Three services explicitly excluded individuals at 25% risk from their predictive testing protocol if the intervening relative was available for testing [39, 44, 57]. Others used strategies to encourage relatives to consider testing, including suggesting the client discuss testing with their relative with the hope that they proceed first [39, 41, 56, 76]; offering to meet the relative and counsel them regarding the consequences of the client having testing first [56]; or to undergo testing alongside their twin sibling [39]. These strategies were useful in two cases [39]. Where these strategies were unsuccessful, clients signed a confidentiality agreement to ensure non-disclosure (to maintain the intervening relative's right not to know) [39, 76]. To minimize adverse outcomes in a case where the intervening relative believed they would commit suicide if they knew they were affected, grandparental blood samples were also collected for use in reproductive testing before revealing the test outcome [76]. The possible adverse effect of testing clients at 25% risk was highlighted in one study: of four intervening at-risk relatives who had been informed of their positive status, three became depressed, and one committed suicide after the result was disclosed [56].

(iv) *Activities involved in genetic counseling practice*

Thirty-five activities involved in contemporary genetic counseling and testing practices for LONDs are summarized in Table 4. Some activities only concerned certain types of genetic testing, while others were consistent across multiple testing settings. All reported activities were performed in one or more predictive testing practices (35/35), whereas fewer were reported in diagnostic (23/35) and reproductive testing (19/35).

(v) *Addressing the goals of genetic counseling*

Eighteen papers included activities that addressed all four goals of genetic counseling (Table 5). The interpretation goal was addressed in fewer than half of the papers (32/69). There were no major differences between the goals addressed and testing types, nor the health professionals involved or location of the practice.

Discussion

The primary aim of this systematic review was to establish a comprehensive understanding of contemporary genetic counseling and testing practices for LONDs.

Table 4 Activities involved in genetic counseling and testing practices for LONDs in accordance with the four defined goals of genetic counseling, and divided between testing types

Genetic counseling activity	Num-ber of papers	References for each testing type		
		Diagnostic testing	Predictive testing	Reproductive testing
<i>Goal of genetic counseling 1: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence</i>				
Assess risk of client and other relatives carrying a pathogenic variant, incorporating family- and variant-specific information, penetrance and pathogenicity in risk assessment	17	[25, 54, 59, 62, 72, 75, 105]	[25-28, 39, 44, 45, 52, 54, 56, 59, 62, 63, 94, 105]	[39, 94]
Gather family history and any relevant family genetic testing reports	15	[62, 68, 72, 93, 101, 103, 105]	[30, 40, 41, 45, 54, 56, 59, 62, 68, 89, 93, 105]	
Gather personal medical history including previous testing results	14	[62, 68, 75, 101]	[27, 30, 40, 45, 54, 55, 59, 62, 68, 89, 105]	[58]
Engage in interdisciplinary discussion and literature review	9	[101]	[30, 39, 48, 49, 52, 55, 59, 102]	[39]
<i>Goal of genetic counseling 2: education about the natural history of the condition, inheritance pattern, testing, management, prevention, support, resources and research</i>				
Provide condition-specific information about:	27	[37, 68, 72, 74, 75, 100, 101, 105]	[27, 30-33, 37, 40, 41, 43, 44, 47, 48, 52, 54, 55, 63, 68, 69, 73, 89, 96, 100, 105]	[100]
Natural history (main clinical symptoms, early and late manifestations, prognosis, mode of inheritance, all possible genetic testing results)				
Uncertainties (variable age at onset, severity, progression, penetrance, mostly limited prevention and treatment options)				
Discuss the use, privacy and storage of results now and in future (e.g. whether they would form part of the medical record, able to be shared in case of death) and distinguish between research and clinical care	17	[54, 62, 74, 75, 101]	[39, 41, 43-45, 48, 49, 52, 54, 57, 59, 62, 74, 89, 97]	[57]
Advise that knowledge about the condition could inform family planning and detail all of the reproductive testing options available	13	[105]	[27, 44, 52, 54, 57, 63, 73, 89, 105]	[29, 51, 58, 98]
Detail the genetic testing process and protocol	12		[27, 33, 40, 42, 44, 45, 48, 52, 57, 71, 73, 89]	[57]
Review possible clinical implications of testing on other relatives	12	[72, 75, 105]	[26, 39, 47, 52, 56, 73, 76, 89, 105]	[39, 51]
Provide information in oral, visual and written format, including online information	12	[62, 93]	[41, 48, 49, 56, 60, 62, 67, 73, 89, 93]	[58, 98]
Gain informed consent in writing	11	[74, 75, 101, 105]	[30, 41, 45, 49, 52, 59, 105]	[58]
Identify and address informational misconceptions, myths and prejudgments	11	[37, 68, 93]	[33, 37, 42, 44, 53, 54, 59, 68, 69, 89, 93]	
Ensure all potential consequences of testing understood by client	7	[93]	[27, 36, 42, 55, 59, 63, 93]	
Discuss possible other implications of testing for the client and relatives (e.g. risk of discrimination in insurance, misattributed paternity)	7	[54, 105]	[39, 41, 47, 52, 54, 63, 105]	
Review limitations of currently available genetic testing	5	[100, 105]	[52, 89, 94, 100, 105]	[94, 100]

Table 4 (continued)

Genetic counseling activity	Num-ber of papers	References for each testing type		
		Diagnostic testing	Predictive testing	Reproductive testing
Review the results of any risk assessment performed as part of the workup	4	[105]	[43, 44, 89, 105]	
Provide information about possible research studies available	1		[73]	
<i>Goal of genetic counseling 3: counseling to promote informed choices in view of risk assessment, family goals, ethical and religious values.</i>				
Discuss motivations for proceeding with testing, including decision-making process, and clarify expectations where required	20	[37]	[27, 30, 31, 33, 37, 41, 44–46, 49, 50, 52, 54, 55, 60, 63, 70, 89, 95, 96]	
Assess psychosocial readiness to undergo testing and ability to cope with testing process and/or either possible result, including adaptation mechanisms, psychological history, current substance abuse/stressors/changes in mood/cognitive functioning	20	[93]	[27, 30, 31, 33, 35, 38, 40, 41, 43–46, 50, 52, 54, 55, 63, 93, 104, 105]	
Assess and address family dynamics and communication (e.g. whether the client plans to communicate any type of result with relatives, suggesting further family discussion before proceeding with testing and/or supporting the client in familial communication)	16	[54, 62, 74]	[30, 39, 41, 44, 45, 48, 49, 52, 54, 55, 59, 62, 63, 89, 96]	[39]
Confirm the client is making an autonomous choice	13			[39, 41]
Review lived experience of disease (e.g. time elapsed since awareness of family diagnosis, whether the client has direct experience and understanding of the disease)	12	[61]	[26, 30, 31, 39–41, 43, 46, 52, 60, 63, 89, 92]	[82]
Discuss the voluntary nature of undergoing testing, including the right to opt-out at any time and alternative options (e.g. DNA banking, deferring testing, undergoing testing but not receiving the results)	10		[27, 30, 41, 43, 44, 46, 49, 52, 59, 71]	
Assess access to social support within and outside the family	10			[39]
Encourage the client to consider possible responses and effects of testing on other individuals (e.g. support person, partners, family members), including the possibility of various results scenarios between different family members	9	[93]	[35, 38–40, 44, 47, 52, 55, 63, 89]	[51]
Review the timing of testing, perceived advantages and disadvantages of proceeding (or not)	8		[26, 28, 48, 52, 55, 63, 89, 93]	
Review common emotional responses and possible psychological effects of testing	8		[26, 42, 44, 45, 52, 55, 89, 96]	[51]
Ensure all potential consequences have been considered	7	[93]	[33, 38, 46, 52, 54, 55, 73]	
Discuss attitudes and values towards family planning options, including termination of pregnancy	4		[27, 28, 42, 55, 59, 63, 93]	[41, 51, 57, 76]
Provide additional consultations when requested and space for the client to raise questions, doubts or concerns	3		[33, 52, 71]	

Table 4 (continued)

Genetic counseling activity	Num-ber of papers	References for each testing type		
		Diagnostic testing	Predictive testing	Reproductive testing
<i>Goal of genetic counseling 4: support to encourage the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder</i>				
Offer counseling or psychological support to client, other family members and support person both pre-, during and post-testing to facilitate adjustment, integrate results into daily life and minimize potential adverse effects	30	[25, 54, 93, 104]	[25-28, 35, 36, 38-41, 43, 44, 46, 48-50, 52, 54-57, 63-66, 71, 93, 95, 104]	[41, 51, 57]
Offer support or information resources throughout (e.g. online information, contact details or referral to relevant organisations)	10	[54, 62, 68, 93]	[40, 48, 52, 54, 56, 60, 62, 68, 73, 93]	
Provide an opportunity for the client to express and explore their emotional reaction to the result	7		[26, 40-42, 54, 55, 63]	
Offer medical follow-up to pathogenic variant carriers	7		[27, 28, 35, 41, 44, 48, 57]	
Preferably the same health provider(s) meet client post-testing	5		[27, 30, 43, 49, 89]	
Request for feedback on the process (e.g. satisfaction with the protocol, general suggestions, if they would recommend it to other persons)	2		[31, 33]	

Sixty-one studies published in 68 papers from 19 countries that described genetic counseling and testing practices for LONDs since 2009 were included. Studies varied greatly in setting and design. HD was the most common condition studied, and predictive testing was examined more frequently than diagnostic or reproductive testing. Although some practices had shared aspects, there were many novel or inconsistent approaches to genetic counseling for LONDs. For predictive testing, a multidisciplinary care approach was taken in most studies, with neurologists, geneticists, and psychologists being the most common health providers involved. Health provider decision-making about genetic testing varied in the presence of ethical issues, high-risk psychopathology, and neurological symptoms. In some predictive testing protocols, up to four pre-test counseling sessions were required. Attendance at follow-up sessions post-testing was variable. Overall, there was an emerging focus on a client- or family-centered, flexible approach to genetic counseling for LONDs to address negative client feedback, possible harms, and barriers to accessing testing. However, few innovative modifications to practice were evaluated. The secondary aim was to identify the extent to which current practices address the established goals of genetic counseling. The findings indicate that current genetic counseling practices rarely address the four published genetic counseling goals.

Given most studies focused on predictive testing, it is difficult to draw any firm conclusions regarding genetic counseling practices for diagnostic and reproductive testing. There are several possible explanations for fewer studies in these two areas. In diagnostic testing, those undergoing testing will demonstrate some symptoms suggestive of a LOND. Therefore, both patients and their health providers may think a genetic test guides medical management and access to emerging targeted clinical trials [77, 78]. Despite this, as the diagnostic testing guidelines for HD note, the confirmation of a disease diagnosis may affect both the patient and their family [15]. Therefore, genetic counseling is an essential part of diagnostic testing. Depending on the patient and their family's needs and expectations, they may need to be informed of hereditary risks, assisted with adjusting to the diagnosis and familial risk or provided with access to predictive or reproductive testing, further support, information, and resources [15, 79]. One crucial difference between LONDs is that for entirely heritable conditions, like HD, a diagnosis would only be confirmed if a pathogenic variant was detected. For partially heritable conditions, like FTD, genetic testing may be performed separately to the diagnosis of the LOND [80]. Different genetic counseling practices would likely be required depending on the patient's diagnostic status and the likelihood of confirming a pathogenic variant [14, 15]. The low number of studies on reproductive testing may be explained by its low uptake rate overall, as

Table 5 Genetic counseling goals addressed in included studies

Characteristics	Number of papers	References for each testing type ^a			
		Diagnostic testing	Predictive testing	Reproductive testing	Unspecified testing type
<i>Goal of genetic counseling addressed in study^d</i>					
Interpretation	32	[25, 54, 59, 62, 68, 70, 72, 75, 93, 99–101, 103, 105]	[25, 30, 32, 39–41, 44, 45, 47–49, 52, 54–57, 59, 62, 68, 70, 76, 89, 93, 94, 99, 100, 105]	[39, 41, 57, 58, 76, 94, 100]	
Education	52	[25, 37, 54, 62, 68, 70, 72, 74, 75, 93, 100, 101, 105]	[25–27, 30–33, 36, 37, 39–45, 47–49, 52–57, 59, 60, 62, 63, 67–71, 73, 74, 76, 89, 93, 94, 96, 97, 100, 105]	[29, 39, 41, 51, 57, 58, 76, 82, 94, 98, 100]	
Counseling	49	[37, 54, 61, 62, 70, 74, 75, 93, 101]	[26–28, 30, 31, 33, 35, 37–50, 52, 54–57, 59–63, 70, 71, 73, 76, 89, 92, 93, 95, 96, 102, 104, 105]	[39, 41, 51, 57, 76, 82]	[34]
Support	45	[25, 54, 61, 62, 68, 93, 101]	[25–28, 30, 31, 33, 35, 36, 38–50, 52, 54–57, 60–66, 68, 71, 73, 89, 93, 95, 102, 104]	[39, 41, 51, 57]	[34]
<i>Number of goals of genetic counseling addressed in study^d</i>					
4	18	[54, 62, 93, 101]	[30, 39–41, 44, 45, 47–49, 52, 54–57, 62, 89, 93]	[39, 41, 57]	
3	18	[25, 68, 70, 75]	[25–27, 31, 33, 42, 43, 59, 60, 63, 68, 70, 71, 73, 76, 105]	[51, 76]	
2	21	[37, 61, 72, 74, 100, 105]	[28, 32, 35–38, 46, 50, 61, 74, 94–96, 100, 102, 104]	[58, 82, 94, 100]	[34]
1	13	[59, 99, 103]	[53, 64–67, 69, 92, 97, 99]	[29, 98]	

^aSome studies had a different number of goals addressed for each testing type, so more than one option could be selected

clients may choose other family planning options like conceiving naturally or choosing not to conceive [81, 82]. Legal barriers to accessing reproductive testing or termination of pregnancy in different regions [44, 57, 58] may also explain the low uptake. Further investigation in both diagnostic and reproductive testing for LONDS is warranted.

The involvement of a multidisciplinary team was consistent across predictive testing practices, which is supported by the current guidelines [9, 11–14]. The low number of studies including genetic counselors suggests this health professional group may be under-utilized. An explanation could be local barriers to incorporating genetic counselors in practice (health-care system disparities, cultural differences, or the global shortage of genetic counselors) [7, 83]. The involvement and role of different health providers were difficult to distinguish in many studies. Only three studies evaluated the benefits of neurologists, psychiatrists, or psychologists in a predictive testing team [30–32]. Where reported, neurological and psychiatric/psychological assessments in predictive testing were more commonly mandatory, which contrasts with the HD predictive testing guidelines, where these assessments are considered important but not required in a predictive testing protocol [9]. In the presence of high-risk psychopathology, neurological symptoms, or ethical issues in predictive testing, health provider decision-making about

proceeding with testing varied. There was no apparent trend to suggest that responses differed between health provider specialty types. Further research is required to compare genetic counseling practices for LONDS between different health providers and assess whether this affects patient outcomes and testing decision-making.

Many studies highlighted the need for an individualized, flexible, client-centered approach to genetic counseling practice, given that a client who attends for genetic testing and counseling has a unique lived experience and motivation for proceeding with testing [25, 39, 41, 45, 55, 63, 69, 76, 82]. Practices should also consider the possible implications of genetic testing for the client's family, given the potential risk of harm for relatives [56, 76], and this is reflected in the current HD predictive testing protocol [9]. Financial, geographical, or language barriers to accessing testing or appropriate support and information may also need addressing [44, 52, 62, 67–69, 73]. Therefore, clients may or may not require a neurological or psychological/psychiatric assessment, a support person at appointments, multiple pre- or post-testing consultations, or further resources, support, or information. Predictive testing performed within an integrated counseling protocol is considered safe in several studies, with few major adverse events reported in clients [46, 84, 85]. Pre-test discussions are thought to protect against adverse

psychological effects post-testing [27, 41, 60]. Few included studies assessed the effectiveness and safety of a modified versus more traditional genetic counseling protocol, highlighting an area of necessary evaluation in the future that is supported by a previous quality assessment on genetic counseling for predictive testing of LONs [86].

Of the studies that did assess innovative genetic counseling practices, there was evidence to support telephone or telehealth consultations for clients to access more flexible testing and support locally [40, 71]. In contrast, the predictive HD testing guidelines, published in 2013, state that results should never be given by telephone [9]. Perhaps this recommendation requires review, given emerging data on telehealth use during the COVID-19 pandemic [87, 88]. Health providers' time may become more limited if a clinical trial for asymptomatic patients becomes available, and interest in predictive testing increases [70, 89]. Still, some may decide not to be tested, as demonstrated by familial amyloid polyneuropathy [33], where disease-modifying therapies are already available, so non-directive counseling remains essential. Additional novel practices, such as using an educational website pre-testing [73] or group sessions post-testing [64–66], may also help manage health provider time. Other innovative approaches to genetic counseling practice should be considered and evaluated, with client safety at the forefront.

All genetic counseling activities were identified in one or more predictive testing studies. In comparison, less activities were identified in diagnostic and reproductive testing (although fewer studies were in these areas). The majority of current practices did not meet all four genetic counseling goals, suggesting that current practices do not reflect the required goals. It is also possible the goals need to be adapted to align with the specific practices required for LONs. Findings do highlight knowledge gaps and considerations for further research in genetic counseling and testing for LONs. The identified genetic counseling activities provide a basis for the requirements of a genetic counseling service delivery model for LONs that addresses all four genetic counseling goals. This model will need to be customized to accommodate the client's specific needs and regional differences in providing care.

Limitations

Limitations exist regarding the individual articles and study selection methodology. The inclusion criteria resulted in the omission of works published in different languages, before 2009 and presented outside peer-reviewed journals. Consequently, no randomized control trials were identified, and eight low-quality studies were not excluded, affecting the robustness of the synthesis. LONs were reported altogether due to their shared similarities, and

therefore condition-specific issues were likely present but not extracted. In addition, studies from 19 countries were included, so there were likely regional differences between genetic counseling practices. Still, aside from the health providers involved and laws that impacted access to genetic counseling and testing, there were no clear country-specific differences.

Firm conclusions or implications for practice are premature, given the overall strength of evidence is low. Although several genetic counseling practices were identified, few were formally trialed or evaluated. There was considerable heterogeneity across the included studies in terms of study design, populations (and response rate), and outcomes. Practices were also inconsistently reported, and some study objectives assessed one aspect of genetic counseling practice only (e.g. knowledge, or motivations to undergo testing). The authors AC and ROS used their knowledge as experienced genetic counselors to combine and allocate genetic counseling activities amongst the four genetic counseling goals, which may have led to a bias toward presenting the aspects of practice considered important to a genetic counselor. Although included practices were assessed regarding addressing genetic counseling goals, it could not be definitively known whether certain practices omitted certain activities due to outcome reporting bias.

Conclusion

Contemporary genetic counseling and testing practices for LONs reveal varied approaches informed by local laws, practices, and resources and the presence of different health providers. Few practices addressed all four goals of genetic counseling. A flexible, multidisciplinary approach to genetic counseling that is adaptable to the client and their family's needs continues to emerge. Evaluations of novel approaches to care are limited and provide an opportunity for further evaluation. Possible future study areas should focus on diagnostic and reproductive genetic testing and counseling practices, and the role and use of different health providers. As genetic testing becomes a routine part of care for patients with LONs (and their relatives), health providers must balance their limited time and resources with ensuring that clients can be safely and effectively counseled, and all four genetic counseling goals are addressed. Increased involvement of genetic counselors or innovative approaches to providing genetic counseling may fulfill this need.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00415-021-10461-5>.

Acknowledgements Thank you to Ana Shah Hossaeni, information services librarian, who assisted with developing the search strategy.

Author contributions AC: study concept and design, major role in the acquisition of data, analysis and interpretation of data, and drafting and revision of the manuscript for content. CJ: study concept and design, revision of the manuscript for content. TN-J: study concept and design, revision of the manuscript for content. ROS: acquisition and analysis of data, revision of the manuscript for content. AME: study concept and design, acquisition and analysis of data, revision of the manuscript for content.

Funding A. Crook received funding for this project from the University of Technology Sydney Chancellors Research scholarship. C. Jacobs, T. Newton-John, R. O’Shea, and A. McEwen report no disclosures relevant to the manuscript.

Availability of data and materials Complete searches and data extraction tables are available in the supplementary information.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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