CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Werner syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Werner syndrome, Werner's syndrome, adult-onset progeria.

1.2 OMIM# of the disease

277700.

1.3 Name of the analysed genes or DNA/chromosome segments

WRN (RECQL2, RECQ3).

1.4 OMIM# of the gene(s)

604611.

1.5 Mutational spectrum

More than 70 disease-causing mutations have been reported.^{1,2} The majority of the mutations are stop codon mutations, splice mutations, or small ins/del that result in truncations of the protein and/or non-sense-mediated decay of mutant mRNA. Several missense mutations that abolish helicase activity or confer protein instability, an intronic mutation that creates a new exon, as well as genomic rearrangements (deletions and duplications) have also been reported.^{1–3} The most common mutation in Caucasian patients is a stop codon mutation in exon 9 (c.1105C>T, p.Arg369Stop), which accounts for approximately 20% of the mutations. There are founder mutations reported among Japanese patients (c.3139-1G>C, which results in skipping of exon 26) and in Sardinian patients (c.2089-3024A>G, which creates a new exon between exons 18 and 19).^{4,5} Potential founder mutations have been reported for Dutch (c.3590delA, p.Asn1197fs), Turkish (c.3460-2A>G, exon 30 deletion) and Moroccan (c.2179dupT, p.Cys727fs) patients.²

1.6 Analytical methods

Standard exon sequencing combined with western blot analysis are performed as routine tests.⁶

1.7 Analytical validation

Sequencing results are confirmed by exon sequencing using different sets of primers. RT-PCR sequencing may be performed to confirm potential splicing mutations. For potential missense mutations, enzyme assays and protein stability may be performed on a research basis using recombinant WRN protein containing the mutations.⁶ If genomic rearrangements are suspected, high-density array CGH can be performed.

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence)

The population prevalence of Werner syndrome is unknown. However, it is likely under-diagnosed because of the lack of awareness of this disorder and the relatively non-specific symptoms (absence of pathognomonic signs).

1.9 If applicable, prevalence in the ethnic group of investigated person

The prevalence of heterozygous carriers in Japan is approximately 1/167 and it is estimated to be approximately 1/120 in Sardinia.^{4,5}

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☒	☐
D. Prenatal	☐	☒

Comment:

This is an adult-onset disorder. The earliest sign is the lack of a growth spurt during adolescence. Onset of a prematurely aged appearance (gray hair, scleroderma-like skin) typically starts in the 20–30 s followed by the appearance of age-related disorders (cataracts, diabetes mellitus, atherosclerosis, cancers, osteoporosis).

Genotype or disease		A: true positives B: false positives	C: false negatives D: true negatives
Present	Absent		
Test			
Positive	A	B	Sensitivity: A/(A+C) Specificity: D/(D+B)
Negative	C	D	Positive predictive value: A/(A+B) Negative predictive value: D/(C+D)

2. TEST CHARACTERISTICS

2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present)

It has not been determined. We estimate that it is >95%.

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2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)

It has not been determined. We estimate that it is close to 100%.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

It has not been determined. We estimate that it is >95%.

2.4 Clinical specificity

(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

It has not been determined. We estimate that it is close to 100%.

2.5 Positive clinical predictive value

(lifetime risk to develop the disease if the test is positive)

It has not been determined. On the basis of the studies of large pedigrees, most, if not all, patients appear to develop symptoms in time. For patients who are tested, and positive for mutations, genetic counselling should be provided for increased risk of malignancies and atherosclerosis and reduced fertility. It is not known whether obligate heterozygotes have increased risk for these disorders.

2.6 Negative clinical predictive value

(probability not to develop the disease if the test is negative)

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

Undetermined. We estimate that it is close to 100%.

Index case in that family had not been tested:

Undetermined. We estimate that it is >95%.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: the tested person is clinically affected

(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No ☐ (continue with 3.1.4)

Yes ☒

Clinically	☒
Imaging	☐
Endoscopy	☐
Biochemistry	☐
Electrophysiology	☐
Other (please describe)	Highly experienced clinicians may be able to diagnose clinically.

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Werner syndrome can be diagnosed clinically, but not solely, using the criteria established by the International Registry of Werner Syndrome (<http://www.wernersyndrome.org>), which divides clinical signs and symptoms into 'cardinal' and 'further' with onset of symptoms after an age of 10 years. Clinical diagnosis may include: ophthalmologic

exam for cataracts, testing for diabetes mellitus, taking a family pedigree and clinical assessment by a clinical geneticist or other physician familiar with Werner syndrome.

An increase in structural chromosomal aberrations (termed variegated translocation mosaicism) in lymphocyte and fibroblast cultures from individuals with Werner syndrome is characteristically observed, but is not diagnostic for the condition.^{7,8}

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Either genetic testing or clinical criteria can miss some individuals with Werner syndrome. Gene testing may be important in patients to confirm the autosomal recessive inheritance, with a low risk to their offspring, compared with atypical Werner syndrome caused by a LMNA mutation, with a 50% risk to each child.⁹

3.1.4 Will disease management be influenced by the result of a genetic test?

No ☐

Yes ☒

Therapy (please describe) *This differs according to the clinical manifestations, but many of the clinical signs of Werner syndrome (cataracts, diabetes, atherosclerosis, skin ulcers) are treatable with standard therapies.*

Identification and treatment of cataracts in the teens or twenties can improve prognosis for vision. There are no reports of treatment of the short stature of Werner syndrome with growth hormone.

Platelet-derived growth factor-BB has been reported to result in some improvement in chronic leg ulcers in WS patient.¹⁰ Bosentan has been reported to be effective in the treatment of digital ulcers in patients with systemic sclerosis, and its use has been recently reported in Werner syndrome patients.^{11,12} Earlier identification and treatment, for example, of soft tissue sarcomas, osteosarcomas, melanoma, and thyroid cancer, may improve prognosis. There is no accepted cancer-screening protocol recommended for Werner syndrome patients, but an awareness of the spectrum of malignancies in Werner syndrome (soft tissue sarcomas, osteosarcomas, melanoma, thyroid cancer) may lead to earlier recognition.

Prognosis (please describe) *A positive genetic test will alert care providers to the diagnosis of Werner syndrome. Median life span of the patients is 54 years,³ 7 years older than in the report in 1966.¹³ Similarly, the median life span of Japanese Werner patients was 53 years.¹⁴ The most frequent causes of deaths are cancers and myocardial infarction.*

Management (please describe) *The results of genetic testing can provide a rational basis for regular medical screening for known, common medical conditions seen in Werner syndrome patients, and increase awareness of potential challenges in treatment. There are case reports of special challenges in, for example, the surgical management of leg ulcers and revascularization procedures in patients with Werner syndrome.^{15,16} Although hypersensitivity to genotoxic agents has been demonstrated in cultured cells derived from patients and heterozygotes, the clinical significance for Werner syndrome patients or carriers with regard to modification of chemotherapy protocols for malignancies has not been established. Clinicians should be aware of the possibility of elevated drug sensitivities to genotoxic agents in this patient population.¹⁷*

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe)

If the result is positive, this confirms the diagnosis of Werner syndrome, and as the manifestations occur over many years, lifestyle changes and preventative measures may be instituted. These include: smoking avoidance, maintaining a healthy weight, treatment of hyperlipidemia if present, and regular exercise to reduce risk of atherosclerosis and type 2 diabetes. Skin care, with avoidance of trauma, and early aggressive treatment of skin ulcers helps to reduce morbidity from this complication. Annual ophthalmologic exam for cataracts, lipid profile, diabetes and hypertension screening are recommended if the diagnosis is confirmed.

If the test result is negative (please describe)

If the test result is negative, this reduces the likelihood of Werner syndrome, and then, atypical Werner syndrome caused by *LMNA* mutations and other causes should be considered. Symptomatic treatment of clinically significant conditions (diabetes, hyperlipidemia, cataracts) is still indicated.

3.2.2 Which options in view of lifestyle and prevention does a person at risk have if no genetic test has been done (please describe)?

No special options; prevention is not possible.

3.3 Genetic risk assessment in family members of a diseased person (To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

If the test is positive and diagnostic, then the unaffected sibs have a 2/3 chance to be a carrier. As in other rare autosomal recessive diseases, they could be tested to determine their carrier status and their partners could be tested to obtain a more accurate recurrence risk. The parents of an index patient with Werner syndrome are obligate carriers, and their sibs or other relatives may also wish to undergo genetic testing to determine their carrier status. Children of a person affected by Werner syndrome are obligate carriers; their partners could be offered genetic testing to obtain a more accurate recurrence risk.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Yes, if the result is negative or uncertain, testing of family members is not recommended.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes, if the index patient has Werner syndrome, then younger family members could undergo predictive genetic testing before the onset of clinical signs and symptoms. As with other predictive genetic testing situations, genetic counselling is strongly recommended before undergoing testing.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Theoretically, but unlikely. Because of the adult onset of the condition, subsequent sibs may already have been born. Because of the autosomal recessive nature of the condition, children of an affected index patient are obligate carriers, but unlikely to be affected.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

Although there is no cure for Werner syndrome, the diagnosis helps to guide appropriate medical management and screening for diseases common in persons with Werner syndrome (regular exams for cataracts, screening for diabetes, atherosclerosis). Treatment in general is similar to the general population. Although elevated sensitivity to genotoxic drugs has been demonstrated *in vitro* in cells derived from WS patients, and heterozygotes, the clinical significance has not yet been determined. Clinicians should be aware of the potential for increased sensitivity to genotoxic drugs.¹⁷ An affected person could learn that his or her children are unlikely to be affected by Werner syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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