European Journal of Human Genetics (2014) 22, doi:10.1038/ejhg.2013.206

www.nature.com/ejhg

CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Huntington's disease

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European Journal of Human Genetics (2014) **22**, doi:10.1038/ejhg.2013.206; published online 9 October 2013

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Huntington's disease (HD) (Huntington's chorea, Huntington disease)

1.2 OMIM# of the disease
143100.

1.3 Name of the analysed genes or DNA/chromosome segments
HTT.

1.4 OMIM# of the gene(s)
143100.

1.5 Mutational spectrum
CAG repeat expansion; for polymorphisms see NCBI accession number NM_002111.6. There are SNPs but no other disease-relevant variations—see: http://www.ncbi.nlm.nih.gov/projects /SNP/snp_ref.cgi?showRare=on&chooseRs=coding&go=Go&locusId=3064.

1.6 Analytical methods
PCR.

1.7 Analytical validation
Parallel analysis of negative and positive controls.

1.8 Estimated frequency of the disease
4–10/100.000 with regional variations within ethnic groups, possibly due to a different genetic background.[1] Recently, it has been suggested that improved clinical and molecular diagnosis of cases, an aging population, and increased general knowledge of the disease has lead to even higher prevalence estimates in Caucasian populations.[2]

1.9 Diagnostic setting

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

Comment:
Invasive prenatal DNA diagnosis is restricted by law in several countries, such as Germany. Pre-implantation diagnosis is technically possible, and it is currently performed, eg, in North America. In several countries, however, PID is restricted by law. Enactment of respective legislation is pending in several other countries.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	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)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
Nearly 100%. Using PCR as an analytical method, there is the possibility of a false negative result in cases with a very large CAG repeat expansion. Therefore, labs might put a disclaimer on results where both repeat numbers appear to be the same, indicating that this testing method could rarely miss a very large expansion.[3]

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Nearly 100%.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
Nearly 100% if family history is informative and symptoms are typical of HD. Notably, however, in some studies over one-quarter of HD patients have a negative family history. In the most comprehensive study to date, up to ~7.8% of patients were determined to be new mutations.[4]

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2.4 Clinical Specificity
(proportion of negative tests if the disease is not present)
There are some rare cases with positive family history of neurodegenerative disease, which is a phenocopy of HD lacking the mutation in the *HTT* gene. We would estimate these cases to amount to <1% (eg, SCA 17 [=HDL4], HDL1-3, DRPLA). Diagnosis may be complicated in rare autoimmune diseases or other syndromes that include choreatic symptoms.[5]

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
Reduced penetrance in allele sizes comprising 36–39 CAG repeats, nearly 100% in allele lengths of ≥40 CAG repeats in average lifespans. The intermediate range between 27 and 35 CAG repeats may disclose a risk of new mutation transmission in offspring, especially when the transmitting parent is a male. There are a very few case reports suggesting a motor phenotype associated with 'intermediate' alleles, but this is a current area of controversy in the field.[6,7] In a large cohort at risk for HD, significant more behavioural abnormalities but normal motor and cognition findings were associated with the 'intermediate' alleles. The behavioural abnormalities were discussed as a prodromal stage of HD.[8]

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:

Nearly 100%.

Index case in that family had not been tested:

Can only be resolved by investigation of the non-affected individual.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected
(To be answered if in 1.9 '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 (in support to clinics if family history is negative)	☒
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	Neuropsychology

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Clinical diagnosis of a typical movement disorder in a patient with cognitive and behavioural impairment as well as evidence of typical atrophy in imaging has a high sensitivity in the diagnosis of HD, when the family history is positive for HD. There are, however, some rare cases of neurodegenerative diseases that can present as phenocopies of HD. Thus, clinical sensitivity and specificity is <100%. Alternate diagnostic procedures are expensive and more time-consuming for the patient, but not harmful.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Alternative diagnostic methods are more expensive and less specific.

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

No	☒
Yes	☐

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.9 '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)

A positive test result has potential impact on family planning and lifestyle, eg, on the choice of education alternatives, professions, career planning etc.

If the test result is negative (please describe)

A negative test result has potential impact on family planning and lifestyle, eg, on the choice of education alternatives, professions, career planning etc.

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)?
The choice to not pursue genetic testing by an at-risk individual will result in a continuation of the 50% risk state, leading to uncertainty and potential impact on family planning and lifestyle, for example, on the choice of education alternatives, professions, career planning etc.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.9 'C' was marked)

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

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

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

3.4 Prenatal diagnosis
(To be answered if in 1.9 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes, but invasive prenatal DNA diagnosis is restricted by law in several countries, such as Germany. Pre-implantation diagnosis is technically possible, and it is currently performed, for example, in North America. In several countries, however, PID is restricted by law. Enactment of respective legislation is pending in several other countries.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

In both, individuals with negative results (potentially due to guilt feelings) or positive results concerning the mutation in the *HTT* gene, the diagnosis can lead to depression and to serious consequences. Thus, detailed counselling, sufficient time to consider all the potential consequences and psychotherapeutic accompany are necessary as recommended in the predictive testing guidelines.[9,10]

CONFLICT OF INTEREST

Carsten Saft received honorarium from Temmler Pharma GmbH & Co.; KG for scientific talks, compensation in the context of the Registry-Study of the Euro-HD-Network, in the context of the ACR16-Study (Neurosearch), the AFQ-Study (Novartis), the Selisistat-Studies (Siena Biotech); and both Carsten Saft and Blair R Leavitt have received research support for research projects from Teva Pharma GmbH and the 'Cure Huntington's Disease Initiative (CHDI) Foundation Inc. Blair R. Leavitt has received compensation in the context of the clinical research studies and/or acted as a consultant to HSG, EHDN, Amarin Neuroscience/Laxdale, MEDA-Corp, Migenix, Prestwick, Siena Biotech, Lundbeck, Bristol-Myers-Squibb, Isis, Novartis, Teva. JTE declares no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by EuroGentest2 (Unit 2: 'Genetic testing as part of health care'), a Coordination Action under FP7 (Grant Agreement Number 261469) and the European Society of Human Genetics.

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