

1 **The use of polygenic risk scores in pre-implantation genetic testing: an**
2 **unproven, unethical practice**

3 Francesca Forzano¹, Olga Antonova², Angus Clarke³, Guido de Wert⁴, Sabine Hentze⁵
4 Yalda Jamshidi⁶, Yves Moreau⁷, Markus Perola⁸, Inga Prokopenko^{9, 10, 11}, Andrew Read¹²,
5 Alexandre Reymond¹³, Vigdis Stefansdottir¹⁴, Carla van El¹⁵, Maurizio Genuardi^{16, 17} on
6 behalf of the Executive Committees and the Public and Professional Policy Committee of the
7 European Society of Human Genetics

8

9 Affiliations and email

10 ¹ Clinical Genetics Department, Guy's and St Thomas NHS Foundation Trust, London, UK

11 francesca.forzano@gstt.nhs.uk

12 ² Department of Medical Genetics, Medical University of Sofia, Sofia, Bulgaria

13 contact.drolgaantonova@gmail.com

14 ³ Institute of Medical Genetics, School of Medicine, Cardiff University, Wales, UK

15 clarkeaj@cardiff.ac.uk

16 ⁴ Maastricht University, Maastricht, the Netherlands g.dewert@maastrichtuniversity.nl

17 ⁵ Human Genetics, Heidelberg, Germany sabine.hentze@embl.de

18 ⁶ Genetics Research Centre, Molecular and Clinical Sciences Institute, St George's University

19 of London, UK. yjamshid@sgul.ac.uk

20 ⁷ ESAT-STADIUS, KU Leuven, Belgium moreau@esat.kuleuven.be

21 ⁸ Institute for Molecular Medicine, Helsinki, Finland markus.perola@thl.fi

22 ⁹ Department of Clinical & Experimental Medicine, University of Surrey, Guildford, United

23 Kingdom i.prokopenko@surrey.ac.uk

24 ¹⁰ UMR 8199 - EGID, Institut Pasteur de Lille, CNRS, University of Lille, F-59000 Lille,

25 France

26 ¹¹ Institute of Biochemistry and Genetics, Ufa Federal Research Centre Russian Academy of
27 Sciences, Ufa, Russian Federation

28 ¹² University of Manchester, Manchester, UK drapr8@gmail.com

29 ¹³ Center for Integrative Genomics, University of Lausanne, CH-1015 Lausanne, Switzerland
30 alexandre.reymond@unil.ch

31 ¹⁴ Department of Genetics and Molecular Medicine, Landspítali University Hospital,
32 Reykjavik, Iceland vigdisst@landspitali.is

33 ¹⁵ Section Community Genetics, Department of Clinical Genetics and Amsterdam Public
34 Health research institute, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The
35 Netherlands cg.vanel@amsterdamumc.nl

36 ¹⁶ Medical Genetics Unit, Department of Laboratory and Infectious Diseases Sciences,
37 Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

38 ¹⁷ Genomic Medicine, Department of Life Sciences and Public Health, Catholic University of
39 the Sacred Heart, Rome, Italy maurizio.genuardi@unicatt.it

40

41 **Abstract**

42 Polygenic risk score analyses on embryos (PGT-P) are being marketed by some private
43 testing companies to parents using *in vitro* fertilisation (IVF) as being useful in selecting the
44 embryos that carry the least risk of disease in later life. It appears that at least one child has
45 been born after such a procedure. But the utility of a PRS in this respect is severely limited,
46 and to date, no clinical research has been performed to assess its diagnostic effectiveness in
47 embryos. Patients need to be properly informed on the limitations of this use of PRSs, and a
48 societal debate, focused on what would be considered acceptable with regards to the selection
49 of individual traits, should take place before any further implementation of the technique in
50 this population.

51

52 **Keywords:** Polygenic risk scores; PRS; PGT; PGT-P; IVF; embryo selection.

53

54

55 **Introduction**

56

57 Polygenic risk scores (PRSs) are estimates of an individual's susceptibility to a specific
58 complex trait obtained by aggregating the effects of dozens, thousands, and potentially
59 millions of genetic variants associated with that specific trait into a single figure. Some
60 private companies have begun to market PRS analyses on embryos to prospective parents
61 through the use of *in vitro* fertilisation and pre-implantation genetic testing (PGT; PGT-P)
62 [1,2,3,4]

63 This practice raises many concerns.

64

65 Complex traits are determined by a combination of genes and environment, and PRSs can only
66 capture a part of the genetic component – that which is derived from the cumulative effects of
67 many genetic variants of small individual effect. PRSs themselves should be calculated using
68 their effects from the ethnic group the parents belong to. The estimation of PRSs for children
69 of parents from diverse ethnic origins is not yet possible to determine correctly. For risks to be
70 calculated as accurately as possible, PRSs should be combined with the effects of non-genetic
71 factors from an individual's life-history such as environment, nutrition, and physical activity.
72 Furthermore, the effects of the genetic factors may interact with each other as well as with
73 changes in lifestyle and clinical risk factors throughout an individual's life, and these
74 interactions may be difficult to account for when calculating the PRS. The concomitant
75 occurrence of rare genetic variants of major effect, whose presence might be unknown, can
76 influence hugely the calculation of the PRS, thus introducing an additional layer of complexity.

77

78 **The PRS situation today – uses and limitations**

79

80 Currently, PRS assessments capture only a fraction of the total estimated heritable component
81 of a trait [5,6], partly because they are determined using only a limited number of polymorphic
82 variants in certain genes. The PRSs are commonly calculated as a weighted sum of the number
83 of disease risk (increasing/decreasing) variants carried by an individual, where the risk variants
84 and their weighting is derived from genome-wide association studies (GWASs) [7,8] may not
85 be the relevant genetic factors but simply located nearby, thus introducing uncertainty in the
86 estimates of effect size associated with individual variants in PRS. The GWASs are typically
87 carried out in populations of defined ancestry (commonly European) and the data extrapolated
88 from those studies might not be valid for populations of different ancestries. As such their
89 general applicability can also be limited.

90

91 Importantly, individual variants may increase the risk for one trait, while simultaneously
92 reducing the risk of another. This complexity is often not obvious to individuals who request
93 information about their future risk through PRS, because they are only informed about the risk
94 for a specific trait that they have sought advice for. They are therefore not provided with data
95 about the risks or benefits of another trait influenced by the same variants, which may or may
96 not be known and might also have included those with effects on prenatal development.

97

98 Given the many limitations summarised above, PRSs are not used in clinics. However, it seems
99 plausible that, in the near future, some may be introduced into clinical assessment with the aim
100 of improving the identification of at-risk individuals, and treatment for specific conditions

101 [9,10]. However, this would not necessarily be translated into implementation for prenatal
102 diagnostics.

103

104 In a proper clinical or research setting, an assessment of all potential contributory risks,
105 including genetic and environmental ones, would be undertaken and made available. Outside
106 of this framework, and especially when PRS assessments are provided as direct-to-consumer
107 (DTC) tests, their evaluation of a patient's risk may be dangerously incomplete and can lead to
108 grave misunderstandings [11,1]. Extrapolating the results from predictive assessments in adult
109 cohorts to use them as a factor for embryo screening would be improper. No clinical research
110 protocol has been performed so far to assess the diagnostic effectiveness of PRSs in embryos.
111 Were these be established, it would take many years to obtain reliable results, given that one
112 might have to wait decades for people to develop, for example, early-onset Alzheimer's disease.

113

114 **The use of PRS in embryo screening and selection**

115

116 While it is relatively common for parents to consider any genetic risks they may pass on to their
117 children, this is normally undertaken via the proven practice of carrier screening and genetic
118 testing for inherited mendelian disorders. In these cases, the ability of the test to predict the
119 development of the disease is usually very high. In fact, when a genetic condition has an
120 extremely low penetrance (the proportion of people with a particular genetic variant who exhibit
121 signs and symptoms of a genetic disorder is low), it is very rare that the prospective parents
122 would even consider prenatal or preimplantation testing.

123

124 When applied to the selection of embryos for transfer, the PRS will relate to an individual
125 family, and not to a wide population. The intrafamilial variability would be much more limited

126 than in the wider population, and therefore the PRS would be unlikely to be useful in
127 determining the choice of one embryo over another, particularly as the number of viable
128 embryos available is typically very small. Even if a discrete difference exists between two or
129 more viable embryos suitable for transfer, a particular combination of genetic variants detected
130 and evaluated would not relate to a definitive diagnosis. Such a set of variants will correspond
131 at best to a small increase in an individual's risk, relative to the population's risk for a complex
132 trait, if the prediction is based on estimates for an ethnic group (ancestry) corresponding to that
133 of the parents. Additionally, if the selection were aimed at more than one PRS per embryo, it is
134 easy to estimate by simple probability that the total number of embryos needed to be examined
135 in order to find at least one (if any) suitable embryos to transfer would be unrealistic for our
136 species and would also be unethical.

137
138 Overall, adding PRSs to PGT would amount to a form of embryo screening. The criteria to
139 assess and implement a screening programme would include, among others, the proportionality
140 principle, according to which 'the possible benefits of the screening should clearly outweigh its
141 possible disadvantages'. For the assessment of the proportionality of PRSs in PGT, it is
142 important to take account of tensions with other parameters, more important for ranking
143 embryos for transfer. Such parameters include viability scores and implications for the complex
144 counselling process, especially when the values of professionals and customers for embryo
145 ranking do not match.

146
147 Research on PRSs is not aimed at the development of pre-symptomatic tests in embryos but
148 rather at the advancement of understanding of disease mechanisms, and the management and
149 treatment of liveborn individuals, most frequently when they reach their adulthood. For PRS

150 research, the aim is different, the population is different, the setting is different from what is
151 expected from PGT.

152

153 **Protecting prospective parents, their offspring, and society**

154

155 At present, carrying out a PRS test for embryo selection would be premature at best. Prospective
156 parents and the public must be provided with adequate and unbiased information on the risks
157 and limitations of such a practice [12]. It will be vital that a societal debate takes place before
158 any potential application of the technique, and this should be focused on what would be
159 considered acceptable with regards to the selection of individual traits, in particular. Without
160 proper public engagement and oversight, the practice of implementing PRS test for embryo
161 selection could easily lead to discrimination and the stigmatisation of certain conditions.

162

163 Further studies are needed to understand which and how polygenic risk estimates for common
164 diseases can be implemented in clinical care. Such research should disentangle the complex
165 interplay between PRSs for a range of conditions and the environment. More studies are needed
166 to understand the biology of normal embryonic and foetal development, as well as its interplay
167 with the intrauterine environment, that is still so elusive.

168

169 For the time being, it is important for reasons of justice to assess whether public and individual
170 resources can be better used to improve our knowledge on PRSs and their relationships with
171 the environment in which we live, rather than on the premature application of an inadequately
172 evaluated test to our future children.

173

174

175 Members of the Executive Committees of the ESHG in 2021 were

176 Maurizio Genuardi (President, Rome, Italy), Borut Peterlin (President-Elect, Ljubljana,
177 Solvenia), Alexandre Reymond (Vice-President, Lausanne, Switzerland), Carla Oliveira
178 (Secretary-General, Porto, Portugal), Karin Writzl (Deputy Secretary-General, Ljubljana,
179 Solvenia), Gunnar Houge (Treasurer, Bergen, Norway)

180

181 Members of the Public and Professional Policy Committee of the ESHG in 2021 were

182 Francesca Forzano (Chair, London, United Kingdom), Angus Clarke (Cardiff, United
183 Kingdom), Christophe Cordier (Lausanne, Switzerland), Guido de Wert (Maastricht, The
184 Netherlands), Sabine Hentze (Heidelberg, DE), Heidi Howard (Uppsala, Sweden), Milan
185 Macek (Prague, Czech Republic), Bela Melegh (Pecs, Hungary), Alvaro Mendes (Porto,
186 Portugal), Yves Moreau (Leuven, Belgium), Markus Perola (Helsinki, Finland), Inga
187 Prokopenko (Guildford, Surrey, United Kingdom), Dragica Radojkovic (Belgrade, Serbia),
188 Emmanuelle Rial-Sebbag (Toulouse, France), Vigdis Stefánsdóttir (Reykjavik, Iceland), Fiona
189 Ulph (Manchester, United Kingdom), Carla van El (Secretary General, Amsterdam, The
190 Netherlands). Observers were: Olga Antonova (Sofia, Bulgaria), Yalda Jamshidi (London,
191 United Kingdom)

192

193 **Conflict of Interest.**

194 The authors declare to have no conflict of interest.

195

196 **Funding.**

197 Professor Inga Prokopenko has received funding by: the World Cancer Research Fund (WCRF
198 UK) and World Cancer Research Fund International (2017/1641), the European Union's
199 Horizon 2020 research and innovation programme (LONGITOOLS, H2020-SC1-2019-

200 874739), the Ministry of Science and Higher Education of Russian Federation (075-15-2021-
201 595), Agence Nationale de la Recherche (PreciDIAB, ANR-18-IBHU-0001), by the European
202 Union through the “Fonds européen de développement regional” (FEDER), by the “Conseil
203 Régional des Hauts-de-France” (Hauts-de-France Regional Council) and by the “Métropole
204 Européenne de Lille” (MEL, European Metropolis of Lille).

205

206

207 **References**

208

209 1. Turley P, Meyer MN, Wang N, Cesarini D, Hammonds E, Martin AR, et al. 2021. Problems
210 with Using Polygenic Scores to Select Embryos. *N Engl J Med.* 2021; 385:78-86

211

212 2. Dalton Conley. A new age of genetic screening is coming — and we don’t have any rules for
213 it. *The Washington Post.* 2021; June 14,

214

215 3. Kyle W. Davis. A New Kind of Embryo Genetics Screening Makes Big Promises on Little
216 Evidence. *Slate.* 2021; July 23

217

218 4. Carey Goldberg. Picking Embryos with best Health Odds sparks new DNA debate.
219 *Bloomberg News.* 2021; 17 September

220

221 5. Janssens ACJW and Joyner MJ. Polygenic Risk Scores That Predict Common Diseases Using
222 Millions of Single Nucleotide Polymorphisms: Is More, Better? *Clinical Chemistry.* 2019; 65:5

223

- 224 6. Wald NJ, Old R. The illusion of polygenic disease risk prediction. *Genetics in Medicine*.
225 2019; 21(8):1705-1707
226
- 227 7. Martens FK, Tonk, ECM, Jansens ACJW. Evaluation of polygenic risk models using multiple
228 performance measures: a critical assessment of discordant results. *Genetics in Medicine*. 2019;
229 21:391–397
230
- 231 8. Wand H, Lambert SA, Tamburro C, Iacocca MA, O’Sullivan JW, Sillari C, et al. Improving
232 reporting standards for polygenic scores in risk prediction studies. *Nature*. 2021; Vol591 11
233 March
234
- 235 9. Lewis CM and Vassos E. Polygenic risk scores: from research tools to clinical instruments.
236 *Genome Medicine*. 2020; 12:44
237
- 238 10. Polygenic scores, risk and cardiovascular disease (2019) ISBN978-1-907198-35-9
239 www.phgfoundation.org
240
- 241 11. Horton R, Crawford G, Freeman L, Fenwick A, Wright CF, Lucassen A. Direct-to-
242 consumer genetic testing. *BMJ*. 2019; 367: 15688
243
- 244 12. Pagnaer T, Siermann M, Borry P, Tšuiiko O. Polygenic risk scoring of human embryos:
245 a qualitative study of media coverage. *BMC Med Ethics*. 2021; 22:125