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1 **Title:** Attitudes towards non-invasive prenatal diagnosis among obstetricians in Pakistan: a developing,  
2 Islamic country

3 **Short Running Title:** Obstetricians' attitudes towards NIPT

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17

18 **Conflict of Interest:** Hussain Jafri is the Director of Medgen Private Limited in Pakistan, a provider of non-  
19 invasive prenatal testing services. All other authors declare no conflict of interest.

20

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22

23 **Attitudes towards non-invasive prenatal diagnosis among obstetricians in Pakistan: a developing,**  
24 **Islamic country**

25  
26 **Abstract**

27 **Objectives:** Stakeholders' views are essential for informing implementation strategies for non-invasive  
28 prenatal testing (NIPT). Little is known about such views in developing countries. We explored attitudes  
29 toward NIPT among obstetricians in Pakistan, a developing Islamic country.

30 **Methods:** A 35-item questionnaire was distributed and collected at eight events (a national conference and  
31 seven workshops in five cities) for obstetric professionals on advances in fetal medicine.

32 **Results:** Responses from 113 obstetrician show positive attitudes towards implementation of NIPT: 95%  
33 agreed prevention of genetic conditions was a necessity and 97% agreed public hospitals should provide  
34 prenatal screening tests. However, participants also agreed the availability of NIPT would increase social  
35 pressure on women to have prenatal screening tests and to terminate an affected pregnancy (53% and 63%,  
36 respectively). Most participants would not offer NIPT for sex determination (55%), although 31% would.  
37 The most valued aspects of NIPT was its safety, followed by its utility, then accuracy.

38 **Conclusion:** Participants generally supported the implementation of NIPT, but raised concerns about social  
39 implications. Therefore, national policy is needed to regulate the implementation of NIPT, and pre-test  
40 information and post-test genetic counselling is needed to mitigate social pressure and support parents to  
41 make informed decisions.

42 **What's Already Known About This Topic?**

- 43 • Non-invasive prenatal testing (NIPT) is being introduced into private prenatal healthcare in  
44 developing countries.
- 45 • Stakeholders' views are essential for informing implementation strategies for NIPT.
- 46 • Little is known about stakeholders' views in developing countries.

47 **What Does This Study Add?**

- 48 • There is a need for a national policy on prenatal screening to regulate the implementation of NIPT.
- 49 • Pre-test information and post-test genetic counselling is essential to help mitigate social pressure and  
50 support parents to make informed decisions.

51

52

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## Introduction

Non-invasive prenatal testing (NIPT) utilizing cell-free fetal DNA in maternal plasma can be used to test for fetal trisomies, fetal Rhesus status, sex chromosome disorders and fetal sex and some microdeletions.

Advances in NIPT technologies are resulting in a rapidly expanding range of testable conditions.<sup>1</sup> NIPT is used mainly to test for the common trisomies, particularly trisomy 21 (Down syndrome), either as the initial screening test, in addition to or instead of combined screening, or as a more accurate test after a high-risk combined screening result (known as contingent screening).<sup>2</sup> Using cell-free fetal DNA, NIPT has high sensitivity and specificity for Down syndrome, and slightly lower sensitivity for Edwards, and Patau syndrome.<sup>3</sup> However, it is not considered diagnostic because it has a positive predictive value (the chance that the child will have Down syndrome) of approximately 80%.<sup>3,4</sup> Furthermore, the performance of cfDNA screening tests is depended on fetal fraction (the amount of the cell-free DNA in the maternal blood that is of fetal origin) and sampling. For example, uninterpretable and non-reportable CfDNA test results due to low fetal fraction in patients carrying aneuploid foetuses can range from 1% to 5%, and sampling errors are reported in 3% and 7% of patients.<sup>5</sup> There is also limited evidence about the performance of cfDNA screening for women of different ethnic origins.<sup>6</sup> Therefore, a positive NIPT result would require confirmatory invasive testing.

NIPT has been commercially available in the USA, parts of Europe, Asia, Africa, Australia and the Middle East for a number of years.<sup>6</sup> It is widely accepted that implementation strategies for NIPT should be based on stakeholders' views, and there is much research on the ethical, legal and social implication (ELSI) of NIPT,<sup>7</sup> generally showing that it is acceptable to various stakeholder.<sup>8,9</sup> However, the simplicity, safety, accuracy and availability of NIPT early in pregnancy raises a number of ethical and social concerns. These include higher uptake of testing and without sufficient consideration,<sup>10,11</sup> women feeling pressured to terminate affected pregnancies and normalisation of selective abortions,<sup>12,13</sup> potential misuse of the

77 technology for less serious or non-medical conditions,<sup>14</sup> and diminishing acceptance of people with  
78 disabilities.<sup>15-17</sup>

79 Doctors are now introducing NIPT into private prenatal healthcare in developing countries, including  
80 the Islamic republic of Pakistan, where there is comparatively little research on the ELSIs of NIPT to inform  
81 implementation.<sup>6,18</sup> Pakistan has a population of over 190 million and is the sixth most populous country in  
82 the world.<sup>19</sup> Genetic conditions are common in Pakistan predominantly because of the favoured custom of  
83 consanguineous marriages.<sup>20</sup> Research on the prevalence of genetic conditions is lacking in Pakistan,  
84 although beta-thalassaemia major is common.<sup>21,22</sup> In Pakistan, only basic prenatal healthcare is provided  
85 through public hospitals, where consultations with doctors are free of charge, but patients may have to pay  
86 for medication and tests, such as routine ultrasound scans (approximately one US Dollar), and there is no  
87 provision of prenatal screening tests. Down syndrome screening is only offered privately by specifically  
88 trained obstetricians (approximately 15-30 US Dollars). Screening involves a nuchal translucency scan for  
89 soft markers, such as, fetal nuchal fold thickness, femur length and absence of nasal bone, without any  
90 biomarkers. Screening is followed by amniocentesis or chorionic villus sampling for patients considered at  
91 high risk of having a child with the condition. The availability of NIPT enables providers to offer an  
92 additional test that is technically more advanced and accurate to those who can afford it (between 480-900  
93 US Dollars). Prenatal screening services have been available in Pakistan's private sector for over two  
94 decades, but there is no national policy governing these services. However, there are fatwas (religious  
95 rulings) placing responsibility on health professionals to determine conditions for which termination of  
96 pregnancy should be offered, albeit privately.<sup>23</sup>

97 Furthermore, research shows that there are differences in stakeholders' (women's and HPs')  
98 preferences for prenatal screening tests between countries, suggesting the need for country specific  
99 approaches to implementing NIPT.<sup>24</sup> Research within developing countries is essential because the

100 implementation of NIPT is likely to be affected by factors such as low priority at policy level, limited health  
101 resources, competing health priorities, lack of trained health professionals, low literacy rates, and cultural  
102 and religious factors.<sup>15,25</sup> Health professionals' views are particularly important because of their role in  
103 developing policy and practice guidelines, introducing new technologies into clinical practice, and  
104 supporting patient choices.<sup>13</sup> Given the paucity of research on stakeholders' views about NIPT in developing  
105 countries,<sup>26</sup> and the recent commercial availability of NIPT in Pakistan, this study aimed to explore the views  
106 of obstetricians in Pakistan about NIPT.

## 107 **Materials and methods**

### 108 **Questionnaire**

109 A self-completion, structured questionnaire developed by Sayres et al. (2011) to explore the views of  
110 obstetricians' attitudes toward implementing NIPT in the United States was adapted for this study.<sup>27</sup> Items  
111 unlikely to work in Pakistan were excluded, such as, "Insurance companies have an obligation to fund  
112 prenatal testing..." because of the lack of availability of such *insurance companies* in Pakistan and items  
113 specific to Pakistan were added (sixth to eighth item on Figure 1). The questionnaire was chosen because it  
114 included both attitudes towards prenatal screening tests more generally and towards NIPT, neither of which  
115 have been previously explored with obstetricians in Pakistan. Our 34-item questionnaire included eight  
116 items on participants' demographics, nine on prenatal screening tests in general (using a Likert scale to  
117 assess agreement or disagreement, see Figure 1) and seventeen on NIPT (eleven using a Likert scale – see  
118 Figures 1 and 2, and 6 using rank ordering – see Figure 3). The questionnaire was only available in English,  
119 the language in which medical degrees are taught in Pakistan, hence did not preclude any potential  
120 participants.

121

### 122 **Data Collection**



146 currently practicing in Pakistan, with characteristics comparable to the demographic of doctors in this field in  
147 Pakistan. Most participants were females (92.9%) and under the age of 36 years (55.8%). Participants'  
148 mean age was  $38 \pm 8$  years. Most participants had been practicing medicine for ten years or less (58.4%).  
149 Participants practiced in public (46%), private (22.1%), public and private (31%), or military (0.9%)  
150 hospitals. Most participants were not currently offering any prenatal screening tests (58.4%). Participants  
151 offering prenatal screening tests offered a nuchal translucency tests using ultrasound technology (with no  
152 biomarkers), and four participants also offered NIPT. See Table 1 for a summary of participants'  
153 demographic characteristics.

154 [Insert Table 1]

### 155 **Perceptions of Prenatal Screening Tests Generally**

156 Most participants believed that women want as much diagnostic information as possible about their  
157 pregnancy (79%) and agreed with women receiving all available prenatal screening tests upon request (82%),  
158 although 11% of participants disagreed (see Figure 1). The majority of participants agreed that prenatal  
159 screening test results significantly affect women's decisions about whether to continue or terminate a  
160 pregnancy (96%) and that this was an appropriate consequence of testing (94%). Participants' views were  
161 divided about whether there were strong social pressures on pregnant women to have prenatal screening,  
162 where 36% of participants agreed, 38% disagreed and 26% neither agreed nor disagreed.

163 Most participants believed that prenatal screening was acceptable in Pakistan (82%) and prevention of  
164 genetic conditions was a necessity (95%). Ninety-seven percent of participants also believed that public  
165 hospitals should provide prenatal screening tests to pregnant women and 99% agreed that genetic counselling  
166 was a necessary component of prenatal screening.

167 [Insert Figure 1]

### 168 **Perceptions of the Implications of NIPT**

169 Only 27% of participants agreed they had a high level of knowledge about NIPT, 43% disagreed and 29%  
170 neither agreed nor disagreed. Nevertheless, most participants also believed NIPT offered value for money  
171 (73%), that the availability of NIPT would encourage clinicians to test more pregnant women (86%) and that  
172 they would offer it to their patients (65%). Ten percent of participants would not offer NIPT to their patients  
173 and 25% were unsure – there was no significant difference in responses between participants working in  
174 public or private hospitals. Most participants acknowledged that women were unlikely to consider the  
175 implication of NIPT at the time of testing (45%), although 31% were unsure and 20% believed they would.  
176 Most participants also believed that the availability of NIPT would increase social pressure on women to  
177 have prenatal screening and to terminate an affected pregnancy (53% and 63%, respectively).

178 When asked about offering NIPT for specific conditions, most participants would offer it for Down  
179 syndrome, other aneuploidy/chromosomal anomalies, and Rh blood group (93%, 90%, 86% respectively).  
180 Most participants would not offer NIPT for sex determination (55%), although almost a third of participants  
181 would (31%) and 14% were undecided (see Figure 2).

182 [Insert Figure 2]

183 Participants also ranked six key aspects of NIPT in order of their importance, with 1 being most  
184 important to 6 being least important (see Figure 3). “No risk to the fetus and mother” was ranked as the most  
185 important aspect of NIPT, with a mean ranking of 2.7 - most frequently ranked as 1 or 2 (23.7% and 36.8%,  
186 respectively). The ease of using NIPT as a “simple blood test” was ranked as the second most important  
187 aspect of NIPT, with a mean ranking of 3.1 and most frequently ranked as 1 by 25% of participants. This  
188 was followed by the high accuracy of NIPT (most frequently ranked as 3) and being able to conducted NIPT  
189 in early pregnancy (most frequently ranked as 4), both with a mean ranking of 3.2. The range of conditions  
190 testable with NIPT was most frequently ranked as 4 or 5, with a mean ranking of 4.1. The cost of NIPT was

191 most frequently ranked as 6 and had the lowest mean ranking (4.7), although a significant minority of  
192 participants ranked this as 1 (13.2%).

193 [Insert Figure 3]

## 194 Discussion

195 Health professionals play a critical role in the clinical implementation of new technologies. Participants in  
196 our study believed that most women want as much diagnostic information as possible and that test results  
197 would significantly affect their decision about whether to continue or terminate a pregnancy, yet women  
198 should receive all available prenatal screening tests upon request. The findings suggest obstetricians support  
199 the prevention of genetic conditions. This may be due to their understanding of women's demand for  
200 prenatal screening tests for various conditions,<sup>28</sup> and experiences of the implications for affected families,<sup>29</sup>  
201 as there is no government provision of medical, social or financial support for such families.<sup>30</sup>

202 Just over half of the participants believed that there are strong social pressures on women to opt for  
203 prenatal screening tests. They also believed that women were unlikely to consider the implications of NIPT,  
204 and that the availability of NIPT would increase social pressure on women to both test and terminate an  
205 affected pregnancy. "Social pressures" are most likely to have been interpreted by participants as being due  
206 to cultural and economic implications of having a child with a disability in Pakistan.<sup>29,31</sup> For example,  
207 parents of children with Down syndrome may experience stigmatisation, social isolation, and rejection of  
208 themselves and/or their affected child by family and community, where negative cultural beliefs include an  
209 affected child being a divine punishment for parents.<sup>29</sup> Pre-test information about the condition and post-test  
210 genetic counselling could mitigate parents' feelings of pressure to opt for NIPT or termination of  
211 pregnancy.<sup>13</sup> However, obstetricians currently offering NIPT in Pakistan provide written information about  
212 the test, but not about the conditions tested for. Similar to others,<sup>32-34</sup> we acknowledge the lack of pre-test  
213 information and genetic counselling as major issues in implementing NIPT, compromising parents'

214 autonomy. Our findings highlight the importance of clinical guidelines on how NIPT should be provided to  
215 parents, including guidance on (a) pre-test information provision so that parents understand the implications  
216 of testing,<sup>34</sup> and (b) provision of post-test genetic counselling for parents at high risk of having an affected  
217 child to enable them to make informed decisions about invasive testing and termination of pregnancy.

218         Similar to others,<sup>35</sup> most of the participants believed that genetic counselling is a necessary  
219 component of prenatal screening. However, we acknowledge the challenges of providing pre- and post-test  
220 genetic information for NIPT in a developing country like Pakistan, because of its low literacy rate and the  
221 lack of government funded prenatal screening or genetic services. Also, in developed countries, midwives  
222 and genetic counsellors/prenatal counselling specialists are usually responsible for the provision pre- and  
223 post-test counselling, respectively. However, in developing countries, this responsibility is most likely to be  
224 the obstetricians'. Furthermore, less than a third of the obstetricians in our study believed they had a high  
225 level of knowledge of NIPT even after a one-hour session on this topic. Whilst we acknowledge that 'a high  
226 level of knowledge' is subjective, this finding may indicate participants' perceptions of their limited ability  
227 to fully understand NIPT, which in turn may be related to poor knowledge on genetics. Therefore, there is a  
228 need for basic genetic education for obstetricians,<sup>13,36</sup> but also for research in developing countries to explore  
229 the most amenable and efficient means of providing pre-/post-test counselling for NIPT.

230         Similar to Pakistan, other developing countries are also likely to lack public hospital infrastructures  
231 for prenatal screening and genetic services. Nevertheless, given the commercial availability of NIPT, with  
232 the potential for testing for a range of conditions, and in light of other genetic technologies likely to be  
233 available in developing countries in the near future (whole genome sequencing), health professionals will  
234 need to be able to translate information for more complicated test results. Therefore, efforts should be made  
235 to ensure that obstetricians have basic genetic education and training in key aspect of genetic counselling.<sup>13</sup>

236 Moreover, participants almost unanimously agreed that public hospitals should provide prenatal  
237 screening tests to pregnant women. Overall, the interest in the prevention of genetic conditions in this  
238 Muslim country highlights the need for debate at policy level to consider (a) strategies for regulating prenatal  
239 genetic technologies in the private sector, and (b) implementing a national antenatal screening policy.<sup>37</sup>

240 The majority of doctors would offer NIPT for Down syndrome, other aneuploidy/chromosomal  
241 anomalies and Rh blood group. This may be because prenatal screening and diagnostic tests are already  
242 available privately for these conditions in Pakistan and termination of pregnancy is acceptable for various  
243 conditions.<sup>28,29,38</sup> Given the emphasis on doctors in Islamic states to decide the conditions for which prenatal  
244 screening, diagnostic tests and termination should be available,<sup>23</sup> further research should explore  
245 obstetricians' attitudes toward a larger range of conditions, including those for which prenatal screening is  
246 not currently available or conditions that could be considered less serious. Such research would inform the  
247 future implementation of more advanced genetic technologies, such as 'Genome-wide NIPT', which is likely  
248 to test for more conditions, including less serious and non-medical conditions.<sup>39</sup> Approximately a third of  
249 doctors were unsure or would not offer NIPT. This may be because NIPT was believed to be too expensive,  
250 and offering it to patients may make them appear interested in profit rather than patient care; and/or because  
251 NIPT would still potentially be followed by invasive diagnostic testing.<sup>40</sup> Further research is needed on  
252 reasons for this finding.

253 The availability of NIPT sex testing enables doctors to identify X-linked conditions, not to offer  
254 termination of pregnancy on the grounds of sex alone. Accordingly, most obstetricians in our study would  
255 not offer NIPT for sex determination, but a significant minority would. The latter finding may be because  
256 the preference for male children is deeply embedded in Pakistani culture,<sup>41,42</sup> yet doctors are not concerned  
257 about the possibility of sex selection leading to an imbalance of sex ratio to males, as observed in countries  
258 like China and India, because abortion on social grounds (including fetal sex) is illegal in Pakistan,

259 religiously impermissible (unless the mother's life is threatened), and culturally disapproved.<sup>42</sup> Nevertheless,  
260 our finding raise concerns about the potential use of NIPT for sex determination and further highlight the  
261 importance of national policy to regulate the implementation of NIPT for medical purposes only.<sup>13</sup>

262 Most studies in developed countries show that health professionals value the accuracy and timing of  
263 NIPT, while women place greater emphasis on test safety and information.<sup>24,43-46</sup> Participants in our study  
264 emphasised test safety, similar to women in developed countries,<sup>13,33,46,47</sup> followed by ease of the test (simple  
265 blood test) and then accuracy. Given the differences in research in developed countries between health  
266 professionals and women, it is important to conduct similar research with women and their partners in  
267 developing countries to ensure that implementation of NIPT also incorporates their needs and preferences.

268 Surprisingly, the cost of the test was given little importance. This may be because the cost would be  
269 to the patient and not to health services, because women are already expected to pay for prenatal screening  
270 test, or because of the financial incentives for private prenatal services. Nevertheless, this raises concerns  
271 about the provision of inequitable health services, where only those with financial resources can afford  
272 prevention of genetic conditions using prenatal screening.<sup>48</sup> This further highlights the importance of  
273 national screening programmes in developing countries to ensure that less privileged families are not further  
274 disadvantaged by lack of access to genetic technologies.

275 The findings should be interpreted with caution as our study was conducted in a large but specific  
276 geographical area with a convenience sample of obstetricians with interest in advances in their field.  
277 Participants were self-selected, therefore, may have had a positive bias towards NIPT. Also, they completed  
278 the questionnaire after a conference/workshop which included a one-hour session on NIPT, which may have  
279 skewed the findings toward a greater interest in NIPT. A study capturing the views of participants nation-  
280 wide and in other developing countries could further enhance our understanding of the ethical and social  
281 implication of NIPT. Nevertheless, this study is the first to explore the views of obstetricians about NIPT in

282 a developing, Islamic country. Qualitative research approaches could provide a more in-depth understanding  
283 of the reasons for the views expressed by the obstetricians in this study. Furthermore, research is needed  
284 with a wider range of stakeholders, including the views of service users and individuals responsible at a  
285 policy level for regulating and developing guidelines for the use of genetic technologies. Nevertheless, our  
286 study with obstetricians highlights the importance of various important points for implementing NIPT in  
287 developing countries.

288 Participants generally supported the introduction of publically funded prenatal screening and the  
289 implementation of NIPT for various conditions, but raised concerns about social implications. They also  
290 highlight the educational and training needs of obstetric professionals and the importance of developing an  
291 infrastructure for the provision of patient information and genetic counselling to mitigate social pressure and  
292 support women to make informed reproductive choices.

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