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Mainstreaming genetics into Italian prenatal care: exploring the future implementation of non-invasive prenatal testing (NIPT) in the Italian National Healthcare System using stakeholder interviews

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ABSTRACT

Introduction Non-invasive prenatal testing (NIPT) has revolutionised the way prenatal testing is performed globally. Italy is one of the European countries considering incorporating NIPT nationwide into the publicly funded healthcare system. Given the extensive autonomy granted to the private sector, that not all technological applications result in equal benefits, and that only a few Italian regions currently offer NIPT through the public healthcare system free of charge, it is crucial to consider how to implement such a technology in the Italian public healthcare sector.

Methods A qualitative study consisting of 12 semistructured interviews was performed. The study population included gynaecologists, geneticists, bioethicists, health economists and public health professionals. Non-probability sampling techniques were used to recruit the study's participants. Content analysis was employed to analyse the data.

Results From the interviews, it emerged that a contingent implementation of NIPT for major chromosomal aneuploidies screening seems the most cost-effective and logical in the Italian context. No consensus was reached on fetal sex and sex chromosome aneuploidies screening. Most interviewees disagreed with making whole-genome/whole-exome sequencing available through the public sector. The high appreciation of NIPT, its potential to advance fundamental objectives of healthcare systems and its compatibility with the Italian prenatal testing culture are among the factors that may facilitate the transition of NIPT from the private to the public sector. Mainstreaming NIPT in the public healthcare system is challenged by its high costs, current offer, lack of prioritisation and regional differences.

Conclusions While transitions take time and are challenging to achieve, this study shows that the current prenatal testing structure and practice would only need modest adjustments to accommodate NIPT, offering hope for the future. Future studies could expand this research by involving a broad range of stakeholders and investigating the effects of various NIPT implementation strategies presently employed across Italian regions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Non-invasive prenatal testing (NIPT) has revolutionised the way prenatal testing is performed globally.

⇒ Italy is one of the European nations considering incorporating NIPT into the publicly funded healthcare system in all Italian regions, as the test is currently offered primarily through private clinics, being paid out of pocket by pregnant women, with only a few regions offering the test through the public healthcare system.

WHAT THIS STUDY ADDS

⇒ To the researchers' knowledge, no study investigated NIPT's mainstreaming into the Italian public healthcare system based on a transition studies perspective.

⇒ This study presents the views of stakeholders arguing for a uniform, contingent and centralised implementation of NIPT across the Italian territory as routine primary obstetrics care for T21, T18 and T13 screening.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study can serve as an initial step in establishing the future implementation structure and practice of NIPT delivery in the Italian context.

INTRODUCTION

Around 6% of infants worldwide are born with a congenital anomaly, leading to hundreds of thousands of related fatalities and representing one of the leading causes of the global burden of illness.[1] Prenatal testing allows for the early detection of congenital anomalies and has thus become an essential component of healthcare systems.[2] Non-invasive prenatal testing (NIPT) allows for the detection of chromosomal anomalies through a maternal

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blood draw, posing no hazards to the pregnant woman or fetus.[3] NIPT is typically performed between 9 and 14 weeks into the pregnancy and can screen for major chromosomal aneuploidies (ie, Patau (T13), Edwards (T18) and Down syndrome (T21)), sex chromosome aneuploidies (monosomy X, XXX, XYY and XXY), clinically significant duplications and microdeletions, and monogenic diseases.[4–6] The test can also determine fetal sex early in gestation and might, in the future, even be used to sequence the fetuses' whole genome, analysing and reporting aberrations on any chromosome.[7–9] NIPT is gaining global acceptance within healthcare systems due to its non-invasive nature and its ability to potentially reduce the necessity for more invasive diagnostic methods.[9] Additionally, prenatal screening programmes are frequently justified by governments, policy bodies and health systems as necessary to enhance reproductive freedom and support informed choices relating to pregnancy.[10] Nonetheless, in many countries, NIPT is still a user-pay screening test and is not publicly subsidised.[9]

'Italy's healthcare system is a regionally based National Health Service (Servizio Sanitario Nazionale, SSN) that provides universal coverage, largely free of charge at the point of service'. (Ferré de B,[11], p 15) Prenatal care services are routinely provided at no cost within the Italian healthcare system. Such services include vaccinations, blood tests, ultrasounds, obstetrical and gynaecological check-ups, pre-eclampsia screening and anaesthesia evaluations.[12] Additionally, expectant mothers have access to certain prenatal screening and diagnostic tests without charge. These include the combined test, which, since 2017, has been made available by the Italian Ministry of Health across all regions for expectant mothers who opt for it, and invasive tests such as amniocentesis and chorionic villus sampling, which are performed exclusively when there is a significant risk of the unborn child having congenital disorders.[13]

Italy is one of the European countries considering incorporating NIPT into the publicly funded healthcare system in all Italian regions, as the test is currently offered primarily through private clinics, being paid out of pocket by pregnant women, with only few regions offering the test through the public healthcare system.[4 14] In 2021, the Italian Superior Health Council designed national guidelines to guide the implementation of NIPT in the Italian public healthcare sector, recommending its use for the screening of T13, T18 and T21 and limiting its offer to those women who are at a higher risk of their fetus being affected by congenital anomalies.[4] However, despite available guidelines endorsing its use, NIPT is not yet part of the Italian benefits package—Livelli Essenziali di Assistenza (LEA)—leaving extensive autonomy to the private sector and to the regional healthcare systems in its offer.

Current debates in the Italian context revolve around the scope of NIPT, whether NIPT should be offered to all pregnant women—universal approach—or confined to specific population groups based on risk—contingent approach.[4] Moreover, it is still unclear how to integrate NIPT into the prenatal care pathway, whom to engage, and if decisions should take place at a regional or national level. These criticalities must be addressed if NIPT is to be mainstreamed in the Italian public healthcare system uniformly across regions, especially as not all applications of the technology offer the same benefits to expectant mothers and their fetuses.[15]

This study presents the perspectives of relevant stakeholders about implementing NIPT in the Italian National Healthcare System. Interviewees are invited to suggest what according to them would be the best implementation strategy in the Italian context, independent of what has been suggested in the most recent NIPT national guidelines. The choice to reflect on aspects beyond those suggested in the latest national guidelines stems from the fact that NIPT is still not uniformly accessible across Italian regions, despite existing guidelines. This requires exploring whether alternative implementation strategies would be better suited to make NIPT more widely available, and, therefore, to mainstream NIPT as an innovation. Thus, our research question is:

How could NIPT be mainstreamed in the Italian Public Healthcare System?

MATERIALS AND METHODS

Theoretical approach

We consider the mainstreaming of NIPT from a transition perspective. Transitions are complex and long-term processes of structural change in societal systems, such as health or energy systems (see Grin *et al*[16] and Köhler *et al*,[17] for overview of the field). Typically, transition management is aimed at responsible implementation of change through systematic and reflexive planning, organising, and applying key steps in desired transitions.[18] Historically, transition theory has proven its merit in clarifying, organising and aiding transitions across various societal domains, such as energy, mobility and waste management and has been applied in analysing the incorporation of genetic services within healthcare systems.

We adopted a transition studies framework by combining elements from the multilevel perspective (MLP, see Geels and Schot[19]) and constellation perspectives (CP, see Van Raak[20]) and operationalising them to the Italian context, as shown in figure 1. Both perspectives are particularly relevant for this research as they offer tools to conceptualise the dynamics of societal transitions. The MLP does so by articulating interactions between three levels of structuration: the microscale 'niche' level where novelty and innovations are located; the mesolevel rules, actors, institutions and technologies that reinforce incumbent system dynamics (the 'regime'); and the large-scale social and material developments that are outside the system of focus but do influence its dynamics (the macrolevel 'landscape'). The CP offers additional insights by describing the dynamics of regimes and niches as societal constellations with a particular function (eg, genetic

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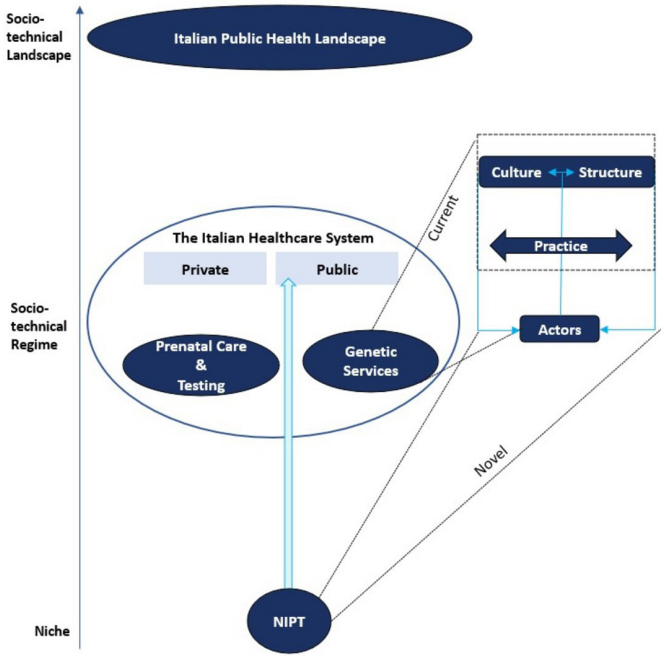

Figure 1 Expanding and adapting the MLP framework to the Italian landscape—the authors' conceptual framework (adapted from Geels; Rigter *et al*[38] and Van Raak).[19 20]

services), the dynamics of which emerge from an interplay of structures (eg, laws, technologies), cultures (eg, values, norms) and practices (eg, routines) that together shape societal dynamics.

The framework in figure 1 was adopted as a starting point to pinpoint the key aspects to focus on when examining the implementation of NIPT into Italy's public healthcare system. The framework builds on established insights from the MLP and CP. The research team synthesised and operationalised the above-mentioned key components from these theories for the context-specific case. Specifically, the chosen framework emphasised the necessity to investigate the possible forces pushing or restraining the transition of NIPT in the public sector, given that these are the dynamics that might support or prevent the mainstreaming of NIPT in the public sector and the external pressures that might stabilise/destabilise the current NIPT offer. Furthermore, components from the MLP and CP were used to shape the data collection and analysis for this study. The study's findings were also employed to propose enhancements to the MLP.

Participant recruitment

The study population included gynaecologists, geneticists, bioethicists, health economists and public health professionals with expertise in the governance of the Italian healthcare system. Participants were recruited using purposive, convenience, and snowball sampling. 10 potential participants were identified by exploring documents from the Italian Ministry of Health, 13 from university and hospital websites, 15 from Italian organisations involving genetics and gynaecology experts, and one through a personal contact who provided access to medical professionals in a specific Italian region. Three additional participants were identified via snowball sampling. The participant recruitment strategy resulted in 42 possible participants who were all contacted via email; 12 agreed to take part in this study. Out of the 30 participants who chose not to engage in the study, none responded to the researchers' email, with the exception of three who cited time constraints as their reason for non-participation. The sampling of the participants ceased once coding saturation was attained. No relationship was established with the participants before the study commencement.

Data collection

A total of 12 semistructured interviews were performed, 11 of which were done online via MS Teams and one via email in written format. All interviews took place between March and May 2023. The interviews were conducted in Italian by the researcher GS, a 21-year-old female with a public health training who was concluding a Master of Science degree at the time of this study and lasted around 40 min. No one else was present during the interviews except the researcher GS and the participant. The creation of the interview guide was carried out by the researchers GS and TV (staff and faculty advisor at the Department of Genetics at University Medical Center (UMC) Utrecht), and KK (assistant professor of politics and governance of sustainability transitions at the Athena Institute, Vrije Universiteit Amsterdam) before data collection based on the concepts highlighted in figure 1 and their inter-relationships. Six main discussion themes were identified (table 1). The interview structure and discussion topics were piloted with colleagues working at the genetics department of UMC Utrecht and adjusted based on the input obtained. Interviews were audio recorded with the permission of the participants, and field notes were taken concurrently and immediately following the interviews.

Data analysis

All interviews were transcribed verbatim in Italian (GS). The transcripts were translated into English (GS) using MS Word's translating option. All interviews were summarised (GS) and, when possible, member checks were conducted. Subsequently, all transcripts were carefully read and coded deductively (GS and TV). The conceptual framework presented in figure 1 served as the foundation for developing the topics, categories and codes used during deductive coding. Three themes, based on the MLP levels, five categories, based on a contextualisation of the MLP levels to the Italian context, nine subcategories and 73 codes resulted from the framework. The researchers combined deductive coding with inductive coding to prevent overlabelling according to predefined categories. Subsequently, GS and TV compared across interviews the responses obtained and provided an overview of the topics and viewpoints expressed throughout the interviews. During this stage, axial coding was

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Table 1 Discussion topics and example questions used during the interviews—interview guide

MLP level	Discussion themes	Example questions
Sociotechnical regime/state of affairs	Current organisation of NIPT in the Italian healthcare system	Who are the actors involved?
		What is your current role in the delivery of NIPT?
		Which facilities are involved? (Private vs public)
		To what extent do private structures have autonomy in choosing the extension of the test that is offered?
		Are there regional differences?
Sociotechnical landscape	Forces hindering or pushing the innovation in the regime	What are the current forces pushing or restraining the mainstreaming of NIPT in the public healthcare sector within your field of expertise?
		Why is there no national NIPT policy/delivery plan?
		Which forces could challenge a uniform adoption of NIPT?
Niche	Technological potential of the test Perceptions surrounding the test	Should pregnant women be allowed to obtain information on any chromosomal anomaly that the test can identify?
		Should the test be limited to screening only a few anomalies (perhaps based on the test's accuracy, risks or ethical issues)? (In other words, for which conditions should the test screen for)
		How is the test currently perceived in terms of usefulness and relative advantage or relative disadvantage compared with other prenatal tests for the detection of chromosomal anomalies?
		How is the test perceived by your field of expertise?
		How willing are you to prescribe NIPT to pregnant women? Under which conditions should this happen (eg, prescribe the test only to high-risk women or to all women)?
		How willing are you to include NIPT in the LEA?
Recommendations/implementation	Mainstreaming NIPT in the Italian public healthcare system Changes at the regime level	In your opinion, how should NIPT be mainstreamed in the Italian public healthcare system? (Only if they believe it is a good idea to do so).
		What should remain in the private realm and what should be offered in the public? Which screenings should be reimbursed or included in the LEA?
		How would the care pathway be? In other words, who should be involved in delivering such a service?
		How should the organisation of the Italian healthcare system change to accommodate NIPT?
		Could you reflect on how NIPT would adapt to or change the current culture, structure and practices of the Italian healthcare system?

LEA, Livelli Essenziali di Assistenza; MLP, multilevel perspective; NIPT, non-invasive prenatal testing.

performed, enabling the researchers to gain a general understanding of the codes that came out of the analysis and the connections between codes and categories.[21]

The researchers used selective coding as the last level of coding to integrate and improve the MLP theory. All data analyses were carried out by using Atlas.ti.

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Quality assurance

The English translations produced by MS Word were verified and corrected/supplemented manually by the researcher GS in case of discrepancies. The procedures conducted during data analysis were conducted by GS and reviewed by TV to increase reliability. The researcher GS coded the Italian transcripts while the researcher TV coded the English translations. The codes used in the English and Italian versions were compared with make sure they were equivalent. Discrepancies in coding were discussed between the researchers until a consensus was reached. This procedure was also crucial in determining whether the English transcripts adequately reflected the content in the Italian transcripts, as variations in coding could stem from translation inaccuracies. Whenever such discrepancies were noted, the researcher GS would reassess the English translations by back-translating them into Italian and scrutinising the congruence with the original Italian texts.

Ethical considerations

Participants were provided with transparent and comprehensive information about the research, including the motivations of the researchers to perform the study and their credentials (i.e., background, affiliation, occupation, etc.), before the start of the interview. After addressing their concerns they were invited to sign informed consent. The interviewees were also asked if they were comfortable with the interview being recorded. Every participant had the freedom to refuse any questions, halt the recording and leave the interview at any time. Anonymity was ensured by referring to the respondents as "interviewee #X", where X is the number assigned by the researcher to each interviewee throughout this study.

To ensure confidentiality and avoid data loss and breaches, the researchers stored all data in a secure environment, namely, the Athena Institute SURFdrive. Only the authors of this study have access to the drive. Interview recordings were transferred on SURFdrive immediately after the interview, paying attention to removing all personal details from the recording. Once uploaded, the recordings were deleted from the voice recorder. All personal data, data traceable to the individual, confidential institutional data, as well as the codes employed for analysis, were stored separately on the researcher's (GS) personal computer. All information will be erased from the SURFdrive 5 years after the completion of this study as according to the VU regulations.

RESULTS

Sample

The group of respondents comprised six gynaecologists, five geneticists and one health economist. Additionally, three of the geneticists had expertise in health policy, and one also possessed knowledge in bioethics. Geographically, the participants were distributed as follows: six from Northern Italy, four from Central Italy, one from Southern Italy and one from an Italian island. Specifically, the distribution of the interviewees by region was as follows: three practised in Lombardy, three in Lazio, two in Emilia-Romagna and one each in Tuscany, Puglia, Sardinia and Liguria. Table 2 categorises the study participants by professional background, geographical area and region in which they conduct their professional activities.

Table 2 Participant details

Characteristics	Participants (n=12)
Professional background*	
Gynaecologists	6
Geneticists	5
Health economist	1
Health policy	3
Bioethicist	1
Geographical area	
Northern Italy	6
Central Italy	4
Southern Italy	1
Islands	1
Region	
Lombardy	3
Lazio	3
Emilia-Romagna	2
Tuscany	1
Puglia	1
Sardinia	1
Liguria	1

*Participants may fall under multiple categories.

Mainstreaming NIPT in the Italian public healthcare system

This section presents the interviewees' reflections on how NIPT could be mainstreamed in the Italian public healthcare sector, depicting what a future regime (future culture, structure and practices) might look like. In doing so, we present the answers provided by the interviewees regarding whether NIPT should be implemented coherently across regions, the possible target population and the scope of NIPT. It is fundamental to note that no reflections are made about the mode of reimbursement of the test as, given the purpose of this study, all interviewees described how NIPT should be implemented if offered free of charge by the Italian healthcare system. Finally, the driving and restraining forces for a transition of NIPT from the private to the public sector are discussed.

National or regional offer

All interviewees agreed that a uniform implementation of NIPT across the whole Italian territory would be desirable, involving both public and private accredited

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facilities. Centralising sample analysis while keeping blood collection sites sufficiently spread across each region has been suggested by six interviewees as a structural change to reduce NIPT-related costs and ensure the test's quality.

> *The goal is not to leave small private laboratories to do these techniques but large structures where large numbers and large samples are concentrated* (Interviewee #2).

Nonetheless, opinions on how centralisation should be accomplished varied among interviewees, with some suggesting setting up three main centres for sample analysis (one in northern, one in central and the other in southern Italy), others setting up one laboratory per region and others setting up one laboratory per interregional area. One interviewee suggested that this should depend on birth rates.

> *In my opinion one laboratory per region, but there are some regions, like Liguria, Val d'Aosta, which do not have many births, so maybe a laboratory per interregional area, I don't know, Northwest, Northeast and South would be the best thing. […]. There are some regions which have so many births like in Campania, Lazio, Lombardy, that they can, that is, one laboratory per region is fine* (Interviewee #12).

Eligible population

Most interviewees suggested that NIPT should be offered to all pregnant women—universal approach—as routine primary obstetric care, with its costs covered by the SSN.

To implement NIPT following a universal approach, two main modes of implementation were suggested, depending on the execution or the dismissal of the combined test. Four interviewees underlined the importance of performing the combined test, or more specifically, a first-trimester ultrasound, either before or after NIPT, without such tests defining the risk boundaries which determine NIPT offer. Contrastingly, two interviewees mentioned that NIPT could be implemented in substitution of the combined first trimester screening test for younger women or for those regions experiencing challenges in guaranteeing the first-trimester screening to all pregnant women.

Despite the widespread agreement that the universal approach seems to be the most desirable, six interviewees—including three who stated that the universal NIPT offer is desirable—suggested implementing NIPT in the Italian public healthcare system following a contingent approach, thus stratifying the population in high, intermediate and low risk. According to such a model, women who fall into a low or extremely high risk will be excluded from NIPT. According to three interviewees, such risk stratification is the most cost-effective and logical approach, given the current structure of the Italian healthcare system, as illustrated below.

> *Regarding whether NIPT should be offered universally or contingently, I don't know if there is any region that is so rich that can think of offering it universally. I don't think there is anyone, even in richer regions like Tuscany, I don't think they can afford to offer it to all'*(Interviewee #12).

Another reason participants mentioned for following a contingent approach, beyond economic reasons, refers to the concern of routinisation and the ethical weight participants attributed to NIPT as a genetic screening test.

> *The prenatal screening pathway is a pathway that has its ethical value […]. The fear of a NIPT offered universally, is that it comes to be understood as just any other screening, like ferritin, TSH, or toxoplasmosis screening, while in fact, this is an examination that involves subsequent choices and a complex pathway about which the woman* has to *be informed beforehand. So, I think this double step [combined test followed by NIPT] is important both in terms of the value of NIPT screening and in terms of the decisions the woman* has to *take* (Interviewee #8).

Contrastingly to the 'solution' of employing a contingent approach to overcome the high NIPT costs, five interviewees highlighted that the price of NIPT strongly depends on test volumes and that therefore, only by having a universal implementation, can the costs of NIPT be lowered.

Defining the scope of NIPT

Most interviewees agreed that NIPT should be offered for free for T13, T18 and T21 screening in the public healthcare sector as these are the most common chromosomal anomalies and allow for survival at birth. Furthermore, the use of NIPT to screen for T13, T18 and T21 has a high detection rate and is strongly supported by scientific evidence. No agreement was reached on whether fetal sex and sex chromosome aneuploidies screening should be included in the public NIPT offer. Specifically, four interviewees advised including fetal sex determination as knowing whether the fetus is male or female helps to identify a series of pathologies linked to the sex chromosomes. Contrastingly, seven interviewees suggested against the inclusion of fetal sex screening in the public offer, given the low clinical utility and the fact that the test may induce sex selection, raising significant ethical concerns. Five participants advocated for the inclusion of sex-chromosome aneuploidies screening in the public offer, given the robust validation studies supporting such NIPT use. Contrarily, five interviewees stated that the sex-chromosome aneuploidies screening lacks adequate validation studies, has a high rate of false positives and poor clinical utility, thus recommending against its inclusion in the public offer.

> *For sex chromosome aneuploidies, there is unfortunately also an ethical issue in the sense that they are not life-incompatible diseases, and they give a lot of false positives […]. Correcting individuals who only have future problems, I don't know how reliable the diagnostics are in that sense* (Interviewee #4).

Nearly all interviewees disagreed with the future practice of making WGS/WES and microdeletions/microduplications screenings available through the public sector. The reasons not to include such extensions are, according

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to the participants, primarily due to a lack of validation studies and clinical evidence and to the poor validity and specificity surrounding such test applications, going against the goal of screening, namely that of reducing the number of women who need to undergo invasive procedures. Furthermore, two interviewees noted that such test applications might find alleles that we are not aware of and may identify a number of genome variations that we do not know how to interpret, potentially inducing selection and '*going against the genetic blueprint of human evolution*' (interviewee #5).

NIPT's transition from the private to the public healthcare sector: driving and restraining forces

Driving forces: enablers

According to eight participants, NIPT has the potential to guarantee high-quality prenatal care given its non-invasiveness, high specificity and sensitivity compared with other biochemical screening tests (tritest and bitest/combined test) currently employed in the Italian public healthcare setting and to lower the number of invasive procedures.

> *I believe that right now, in terms of precision and accuracy, NIPT is unrivaled* (Interviewee #3).

> *From an ethical point of view, NIPT is great because it does not put at risk a possible spontaneous termination of pregnancy due to the invasiveness of the procedure* (Interviewee #9).

Aside from the high appreciation of NIPT, it was highlighted that its introduction into the public sector would not cause cultural or ideological problems but match the widespread current prenatal testing culture, representing another facilitator. One participant also stated that NIPT's implementation in the public healthcare system would not raise any significant ethical concerns, as these would be similar to those surrounding other prenatal tests now used in Italy. Additionally, according to one interviewee, NIPT's introduction into routine prenatal care would help address the low birth rates that currently affect the country.

> *Today there is a strong movement with respect to low birth rates in our country, so all measures that facilitate, let's say, the pregnancy pathway are beginning to be viewed favorably by administrators*' (Interviewee #8).

Last, participants felt that the mainstreaming of NIPT throughout all Italian regions is crucial, as the current test offer fosters a kind of discrimination that is unacceptable and contributes to low-quality prenatal care. Specifically, according to the participants, the fact that some regions provide NIPT testing for free while others require the woman to pay the whole test expense generates regional disparities in access to care. Such differences in access to care also concern the public sector as, due to the regionalisation of the Italian healthcare system, even if some regions have decided to offer NIPT via the public healthcare sector these have done so differently (ie, delivering the test to different target groups and with a different extension). What is more, as highlighted by three interviewees, is that even if two regions offer NIPT exclusively to those women who, for example, following the combined test show an intermediate risk, the boundaries defining that risk may vary between regions. Additionally, there are serious ethical problems in regions where NIPT is only available in the private sector or as a solvent activity since this mode of delivery encourages less wealthy women to undergo an invasive procedure while allowing more wealthy ones to access the test, further exacerbating existing inequalities.

> *A fundamental problem is that of unequal access [to NIPT] and therefore the ethical implications of not giving all women the same opportunity. This is one of the problems that is due to regionalization. This is true also in many other areas. […]. So, this is a general type of problem of Italian national healthcare* (Interviewee #2).

Most importantly, almost all participants indicated that the NIPT offer and scope in the private sector depend on purely commercial logic and financial agreements rather than motivated by scientific evidence or clinical utility.

> *Although the Italian guidelines for NIPT explicitly state that DNA testing cannot replace the combined test, it can be anticipated or done at the same time as the combined test, but it cannot be replaced, in the private sector there is a large portion of gynecologist who don't do the combined test but do the DNA test directly with disastrous results because, unlike in the past, when we used to diagnose conditions like anencephaly, gastroschisis, or omphalocele in the first trimester, we now diagnose such conditions later in the pregnancy. This is not a development* (Interviewee #6).

According to one interviewee, this inappropriate use of NIPT has serious ramifications in the Italian public healthcare sector as when the test detects 'atypical' chromosomal anomalies, gynaecologists working in private practices often lack the necessary knowledge and an internal clinical pathway to perform subsequent analysis and manage the patient, thus redirecting the women to public facilities. However, according to the same interviewee, women frequently do not meet the criteria to access future examinations in the public healthcare system, as the wide application of NIPT is not supported by national guidelines.

Restraining forces: barriers

All interviewees suggested that one of the most important barriers to NIPT's implementation in the Italian public healthcare sector is its high costs. Such high costs, according to one interviewee, make it hard to conceptualise NIPT as a screening test, as the purpose of a screening test is that of screening the whole population at low costs.

Another factor holding back a public NIPT offer in Italy, according to four interviewees, has to do with its non-prioritisation by the Ministry of Health and relevant national bodies involved in its mainstreaming. Specifically, despite the publication of the 2021 national guidelines, little has changed to date from the standpoint of

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the regions' transposition of this information. Such poor receptiveness, according to the participants, can be traced to the fact that this document never became decree law, which is an essential step for guidelines to be adopted and followed by all regions. Furthermore, two interviewees highlighted that the Italian Ministry of Economy and Finance has not yet set a budget for this screening test, contributing to such poor transposition and the lack of inclusion of NIPT in the LEA.

> *Actually, in the LEAs, in the nomenclator, any research on aneuploidies, conducted in any way, without specifying the technique, is already expected to be offered; therefore, there is the place in which NIPT could be introduced into the LEAs. […]. However, there is no established tariff for the test, so it is not applicable* (Interviewee #12).

According to many, regionalisation represents another factor that impedes the transition of NIPT in the public sector. Specifically, according to one interviewee, the fact that each region independently decides how to implement NIPT national guidelines in regional protocols does not help NIPT's mainstreaming. Moreover, three interviewees noted how regional differences in financial assets may impede the implementation of NIPT in the public healthcare sector. In fact, even if it would be established at the national level that the regions have to give NIPT for free, if one region does not have the necessary funds, they will not do so, as suggested by one interviewee.

> *National guidelines for NIPT exist. The first problem now is whether there is economic autonomy in each region. And second, the way these guidelines are then ultimately implemented in regional protocols. I don't know why everyone does their own thing* (Interviewee #6).

By contrast, one interviewee emphasised how, in the Italian context, there is equity in the distribution of national health system resources; in other words, the amount of money allocated per resident is the same across regions along with the citizen's rights. However, due to variations in institutional capital and economic and social development, some regions with the same amount of funds are less productive than others. Thus, the interviewee did not envision regionalisation as being a barrier.

Another barrier to NIPT's mainstreaming, according to one interviewee, is the current use of the combined test for the detection of both fetal chromosomal anomalies and pregnancy complications, as administrators may be prone to think that the combined test can detect more at a lower cost. Nonetheless, this barrier was not widely recognised among this study's participants. Lastly, two interviewees noted that the current NIPT offer, specifically the strong economic interests of private groups, prevents NIPT's transition into the public sector.

DISCUSSION

This study highlights that mainstreaming the NIPT niche is a complex endeavour, in particular, because potential pathways for mainstreaming are manifold. For instance, the population to whom the test should be offered and the conditions the test should screen are not easily determined. This is especially true as, when viewing the results of this research from a transition studies perspective, the regime, and consequently the location and current delivery of NIPT within the Italian healthcare system, is challenging to describe, given the extensive diversity that characterises NIPT offer in both the public and private sectors. Based on the interviews conducted, it can be concluded that a uniform, contingent and centralised implementation of NIPT across the Italian territory as routine primary obstetrics care would be desirable for T21, T18 and T13 screening. In line with the existing Italian healthcare regime, this would not be a universal strategy like the Netherlands, but rather similar to its European predecessors UK, Germany and France.[22 23]

Such a result matches and expands the most recent 2021 national guidelines concerning the mainstreaming of NIPT in the Italian public healthcare sector. Specifically, the most recent cost-effectiveness analysis conducted by the Italian Superior Health Council, highlights that a contingent approach would lead to a healthcare spending increase between €13 and €18 million.[4] This is in stark contrast to the €100 million surge anticipated with universal adoption, corroborating this study's conclusion that a contingent approach is the most prudent and cost-effective for Italy.[4] Furthermore, starting with a contingent approach, with coherent risk boundaries across regions, to later expand to a universal offer of NIPT, would be the most logical implementation mode considering that currently not all regions have integrated NIPT into the public sector and asking such regions to start with a universal NIPT offer might lead to poor adherence. It is imperative that all regions are able to conform to the proposed implementation plan to guarantee uniformity throughout, which is fundamental from the standpoint of care and fairness. Similarly, the utilisation of NIPT solely for the screening of major chromosomal abnormalities in public healthcare appears the most appropriate strategy as a wide application of the test, at least presently, would increase the costs associated with it, making it less implementable and free of charge by regions. In the context of this research, it is pivotal to understand that interviewees were not totally against, for instance, a wide expanded scope of the test, but rather that such applications are offered for free in the public sector, given their lower accuracy levels and the need of providing services that have a 'guarantee' in the public sector. The interviewees' argument for excluding a wide expanded scope of the test from the public offering, due to the lack of such a guarantee, aligns with the arguments of van der Meij *et al*[22] who also highlight a lack of studies surrounding a wide application of the test. Most importantly, this research revealed how the values of the Italian healthcare system, the most important being free access to and high-quality care, demarcate the level of risk professionals are willing to accept in screening chromosomal

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anomalies, being a significant finding. Additionally, this research revealed that, in the Italian context, the value of prenatal testing resides in minimising the number of invasive procedures rather than establishing the presence of all potential chromosomal disorders, justifying the need for applications of the test with high accuracy.

This study also identified several facilitators that could support the transition of NIPT to the public healthcare system. These include the high appreciation surrounding NIPT, its potential to advance fundamental objectives of healthcare systems—such as enhancing and securing equitable access, affordability and widespread availability of prenatal testing and care on the national territory—encourage pregnancies, and its compatibility with the Italian prenatal testing culture. Such findings are consistent with studies which have shown that NIPT users and healthcare professionals have positive attitudes towards NIPT.[24–26] The reasons for this high level of appreciation, van der Meij *et al*[27] pointed out, are the non-invasiveness, accuracy and early application of NIPT, being comparable to the justifications given by this study's participants. Work on women's perspectives on NIPT also stresses the importance of responsible, ethical and financially fair implementation of NIPT.[28] The claim that NIPT may reverse low birth rates, contrasts with ethical concerns surrounding the test's use and an increase in pregnancy terminations.[29 30] In Italy, Law 194/1978 governs the termination of pregnancy, decriminalising abortion up to the 12th week. This decriminalisation period falls within the 9th–14th week time frame for conducting NIPT, which may raise significant concerns. However, it is pivotal to realise that the implementation mode of NIPT along with the cultural context in which NIPT is implemented impacts the relationship between NIPT use and pregnancy termination rates. For instance, sex-selective termination of pregnancy has had several detrimental demographic repercussions in countries such as China and India, leading such countries to outlaw prenatal fetal sex determination.[9] Contrastingly, Hill *et al*[31] investigated the effect of NIPT on termination of pregnancy in relation to Down syndrome, suggesting that pregnancy termination rates decreased or remained unchanged compared with rates recorded prior to the introduction of NIPT. Thus, performing pilot studies in the Italian context or analysing existing regional data on different NIPT implementation strategies could give a more precise indication of such a relationship.

The facilitators mentioned above may destabilise the existing regime, creating a window of opportunity for NIPT's mainstreaming into public healthcare. Nonetheless, NIPT's high costs, its current offer, regional variations, the way national guidelines are implemented in regional protocols, and the lack of prioritisation of NIPT on behalf of the Ministry of Health and relevant national bodies involved in its mainstreaming all represent significant challenges that must be overcome. In this regard, our participants confirmed Ferré *et al*'s[11] argument that regionalisation poses a considerable obstacle to successfully implementing technologies uniformly across the Italian territory. When viewed from a transition studies perspective, such restraining forces span all three levels of the MLP stabilising the existing regime and preventing niche-upscaling.[19]

In facilitating the transition of NIPT from niche to regime, and overcoming the barriers identified by this study, it is essential, according to transition management, to establish long-term visions supported by multiple actors involved in the transition process.[18] In formulating such visions, the Italian government can take up the leading role, not by imposing change but rather by encouraging collective learning processes and the participation of actors at the national and regional levels.[32] The participation of actors in developing implementation strategies is fundamental to maximise the adoption of implementation guidelines as, as illustrated by this research, the creation of national guidelines is insufficient. This research can serve as an initial step in fostering such dialogue, suggesting that the NIPT is implemented, at least initially, as a test reserved for a specific subpopulation and solely for screening major chromosomal aneuploidies. Starting with such approaches would enable reflexive activities, evaluating the proposed implementation strategies, monitoring progress and leading to visions' adjustment and best practices establishment.[17] Following the establishment of such practices and pertinent national guidelines, it is crucial that such guidelines are taken up by the Minister of Health and the State-Region Conference to ensure their transposition in regional protocols. Additionally, the Italian Ministry of Economy and Finance should set a tariff for this test and establish whether NIPT qualifies as an LEA.

Finally, this study also carries important insights for the transition studies field. Specifically, this study reiterates the importance of the 'spatial turn' in the field by stressing that when governing regionalised (healthcare) systems it would be more accurate and fruitful to pay attention to (the spatially localised context of) multiple regimes and their interactions rather than conceptualising the regime as homogeneous, highlighting the MLP's challenges in accounting for local geographies.[33 34] This also requires interrogating the capacities of (national) governments for accelerating translocal transition dynamics in and between multiple regional (innovation) systems in light of national policy ambitions.[35]

Strengths and limitations

The authors' choice to discuss the mainstreaming of NIPT from a transition studies perspective, by employing solid and validated theories such as the MLP and CP, originates from the extensive use of such frameworks in studies on healthcare systems, including studies on the integration of genetic services in healthcare systems.[36 37] This increases the study's validity. Moreover, the use of an interview guide and quotes throughout the results section, the member checks of interview summaries and the comparison/complementation of the study's findings

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with previous literature increase this study's validity and credibility.

Nonetheless, the small sample size of this research and the fact that most of this study's respondents operated in northern and central Italy and in facilities belonging or accredited to the SSN affect the generalisability of the findings. Additionally, the fact that one interviewee chose to provide their responses in written form, might have influenced the richness of the data of that particular interview.

CONCLUSIONS AND FUTURE RESEARCH

This study sought to explore how NIPT could be mainstreamed in the Italian public healthcare system from a transition study perspective. Based on 12 semistructured interviews, our study indicates that the most logical approach in the Italian context is implementing NIPT, at least initially, as a test reserved for a specific subpopulation identified by a combined test and employing the test solely for screening major chromosomal aneuploidies. Such an approach would fit well with the structural elements of the Italian healthcare system, the current NIPT delivery structure and practice, and the cultural values inherent to the Italian healthcare system and prenatal testing.

While transitions take time and are challenging to achieve, particularly in healthcare systems, this study showed that the current prenatal testing structure and practice would only need modest adjustments to accommodate NIPT, offering hope for the future. Studies into women's perspectives on ethical issues regarding NIPT implementation stress the importance of deliberative engagement in research and policy on morally complex innovations.[28] Future studies could expand these lines of research by including the knowledge and perspectives of a broader range of stakeholders, such as pregnant women, and by investigating the effects of various NIPT implementation strategies presently employed across Italian regions, along with the practice and structure behind them.

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REFERENCES

1 World health organization (WHO). Congenital disorders. World Health Organization; 2021. Available: https://www.who.int/health-topics/congenital-anomalies#tab=tab_1 [Accessed 19 Jun 2024].
2 Tamminga S, van Maarle M, Henneman L, *et al*. Maternal Plasma DNA and RNA Sequencing for Prenatal Testing. *Adv Clin Chem* 2016;74:63–102.
3 Lo YMD, Corbetta N, Chamberlain PF, *et al*. Presence of fetal DNA in maternal plasma and serum. *The Lancet* 1997;350:485–7.
4 CSS Sezione I. *Screening del DNA fetale non invasivo (NIPT) in sanità pubblica*. 2021.
5 Grati FR, Molina Gomes D, Ferreira JCPB, *et al*. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenat Diagn* 2015;35:801–9.
6 Wong FCK, Lo YMD. Prenatal Diagnosis Innovation: genome Sequencing of Maternal Plasma. *Annu Rev Med* 2016;67:419–32.
7 Lord J, McMullan DJ, Eberhardt RY, *et al*. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. *Lancet* 2019;393:747–57.
8 Alberry MS, Aziz E, Ahmed SR, *et al*. Non invasive prenatal testing (NIPT) for common aneuploidies and beyond. *Eur J Obstet Gynecol Reprod Biol* 2021;258:424–9.
9 Bowman-Smart H, Savulescu J, Gyngell C, *et al*. Sex selection and non-invasive prenatal testing: a review of current practices, evidence, and ethical issues. *Prenat Diagn* 2020;40:398–407.
10 Ravitsky V. The Shifting Landscape of Prenatal Testing: between Reproductive Autonomy and Public Health. *Hast Cent Rep* 2017;47:S34–40.
11 Ferré deB, Valerio L, Lazzari F, *et al*. *Health System Review 2014*. 4th edn. 16. Italy: Health Systems in Transition, 2014.
12 Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico. Il calendario di visite e esami: mangiagalli center. Available: https://www.policlinico.mi.it/mangiagalli-center/diventare-mamma/calendario-visite-e-esami-gravidanza [Accessed 20 Jun 2024].
13 Ministero della Salute. Banche Dati E Anagrafi. Available: https://www.salute.gov.it/BancheDati/anagrafi/GDA [Accessed 20 Jun 2024].
14 Gadsbøll K, Petersen OB, Gatinois V, *et al*. Current use of noninvasive prenatal testing in Europe, Australia and the USA: a graphical presentation. *Acta Obstet Gynecol Scand* 2020;99:722–30.
15 Suciu ID, Toader OD, Galeva S, *et al*. Non-Invasive Prenatal Testing beyond Trisomies. *J Med Life* 2019;12:221–4.

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16 Grin J, Rotmans J, Schot J. *Transitions to sustainable development: new directions in the study of long term transformative change*. New York, NY: Routledge, 2010.
17 Köhler J, Geels FW, Kern F, *et al*. An agenda for sustainability transitions research: state of the art and future directions. *Environ Innov Soc Transit* 2019;31:1–32.
18 Loorbach D. *Transition management: new mode of governance for sustainable development*. Utrecht, the Netherlands: International Books, 2007.
19 Geels FW, Schot J. Typology of sociotechnical transition pathways. *Res Policy* 2007;36:399–417.
20 van Raak R. *Transition policies, connecting system dynamics, governance and instruments in an application to dutch health care*. Erasmus Universiteit Rotterdam (EUR), 2016.
21 Gray DE. *Doing research in the real world*. London: SAGE Publications, 2018.
22 van der Meij KRM, Sistermans EA, Macville MVE, *et al*. TRIDENT-2: National Implementation of Genome-wide Non-invasive Prenatal Testing as a First-Tier Screening Test in the Netherlands. *Am J Hum Genet* 2019;105:1091–101.
23 Perrot A, Horn R. The ethical landscape(s) of non-invasive prenatal testing in England, France and Germany: findings from a comparative literature review. *Eur J Hum Genet* 2022;30:676–81.
24 van Schendel RV, Kleinveld JH, Dondorp WJ, *et al*. Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening. *Eur J Hum Genet* 2014;22:1345–50.
25 Hill M, Johnson J-A, Langlois S, *et al*. Preferences for prenatal tests for Down syndrome: an international comparison of the views of pregnant women and health professionals. *Eur J Hum Genet* 2016;24:968–75.
26 Benachi A, Caffrey J, Calda P, *et al*. Understanding attitudes and behaviors towards cell-free DNA-based noninvasive prenatal testing (NIPT): a survey of European health-care providers. *Eur J Med Genet* 2020;63:103616.
27 van der Meij KRM, Njio A, Martin L, *et al*. Routinization of prenatal screening with thenon-invasive prenatal test: pregnant women's perspectives. *Eur J Hum Genet* 2022;30:661–8.
28 Vanstone M, Cernat A, Nisker J, *et al*. Women's perspectives on the ethical implications of non-invasive prenatal testing: a qualitative analysis to inform health policy decisions. *BMC Med Ethics* 2018;19:27.
29 Dufner A. Non-invasive prenatal testing (NIPT): does the practice discriminate against persons with disabilities? *J Perinat Med* 2021;49:945–8.
30 Haidar H, Vanstone M, Laberge A-M, *et al*. Implementation challenges for an ethical introduction of noninvasive prenatal testing: a qualitative study of healthcare professionals' views from Lebanon and Quebec. *BMC Med Ethics* 2020;21:15.
31 Hill M, Barrett A, Choolani M, *et al*. Has noninvasive prenatal testing impacted termination of pregnancy and live birth rates of infants with Down syndrome? *Prenat Diagn* 2017;37:1281–90.
32 Rotmans J, Kemp R, van Asselt M. More evolution than revolution: transition management in public policy. *Foresight* 2001;3:15–31.
33 Coenen L, Benneworth P, Truffer B. Toward a spatial perspective on sustainability transitions. *Res Policy* 2012;41:968–79.
34 Fuenfschilling L, Truffer B. The structuration of socio-technical regimes—Conceptual foundations from institutional theory. *Res Policy* 2014;43:772–91.
35 Kok KPW, de Hoop E, Sengers F, *et al*. Governing translocal experimentation in multi-sited transition programs: dynamics and challenges. *Environ Innov Soc Transit* 2022;43:393–407.
36 Broerse J, Grin J, eds. *Toward sustainable transitions in healthcare systems*. 1st edn. New York, NY: Routledge, 2017.
37 Vrijenhoek T, Tonisson N, Kääriäinen H, *et al*. Clinical genetics in transition-a comparison of genetic services in Estonia, Finland, and the Netherlands. *J Community Genet* 2021;12:277–90.
38 Rigter T, Henneman L, Broerse JEW, *et al*. Developing a framework for implementation of genetic services: learning from examples of testing for monogenic forms of common diseases. *J Community Genet* 2014;5:337–47.

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