Introduction
Non-invasive prenatal testing (NIPT) of cell-free fetal DNA has been entering and transforming prenatal care rapidly during the last three years, which led to a number of position statements in relation to practical standards for NIPT services from professional organisations [1–4]. At the moment, NIPT is recommended for high-risk pregnancies only, but recent studies tend to confirm good results also in low-risk populations, at least for trisomy 21 [5]. NIPT-related research in large part focuses on the testing methods, their accuracy, validity and implementation in general. However, studies and case reports with the aim to discover potential pitfalls for NIPT services regarding individual decision making and counselling in daily practice are still underrepresented. The existing studies are often hard to compare due to highly variable implementation processes and differing national regulative frameworks for prenatal testing [6]. While, for example, the UK or the Netherlands proactively have established national boards and research programs [7, 8] in order to shape and monitor the implementation of the emerging technology, no such action has been taken in the majority of countries – among them Germany, where the first provider entered the market in 2012. This is particularly noteworthy, since NIPT has been defined as a genetic examination in accordance with the German Genetic Diagnostics Act (GenDG), which means among other things that a special training in genetic counselling issues is required from the offering gynecologists. Apart from other NIPT-related aspects like the validity of the test, this is a serious problem for the implementation process in almost all countries. Studies from several countries are indicating that there are substantial educational gaps with regard to the limitations of NIPT also among maternal-fetal medicine (MFM) spe-

Abstract
While NIPT is being implemented rapidly, the implementation of a corresponding specialized counselling process in many respects lags behind. As a consequence, legal requirements and other testing conditions sometimes are not fulfilled adequately. The reported case illustrates the importance of trained personnel in the counselling and NIPT process and shows so far neglected risks for the pregnant woman and her reproductive autonomy.

Zusammenfassung
Während der nicht invasive pränatale Bluttest (NIPT) unaufhaltsam Einzug in die Praxis hält, hinkt die Implementierung eines darauf abgestimmten Beratungsprozesses in vielen Bereichen noch hinterher, sodass gesetzliche Regelungen und andere Testvoraussetzungen nicht immer eingehalten werden. Der hier beschriebene Fall eines Spätabbruchs nach missglücktem NIPT-Einsatz zeigt die Notwendigkeit von aktuellem Fortbildungsstand und Expertise bei den Anbietenden sowie die Risiken für die reproduktive Autonomie, wenn diese Bedingungen nicht erfüllt sind.

The Case of a Late Detected Trisomy 13 Reveals Structural Problems in NIPT Counselling and Highlights Substantial Risks for the Reproductive Autonomy

Nicht invasiver pränataler Bluttest (NIPT): Experten gefragt!
Der Fall einer spät entdeckten Trisomie 13 offenbart bezüglich der Beratung und bei der Implementierung des neuen Tests strukturelle Probleme, die Risiken für die reproduktive Autonomie der Frau bergen

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cialists [9], and these gaps are likely to be even more significant among non MFMs. The following case may show this assumption in an unsettling clarity.

Case

B., a 36-year-old healthy woman (with an 11-year-old child) got pregnant in a new partnership. Her gynecologist – she knew him as being generally reluctant to do prenatal diagnosis beyond basic ultrasound (as a part of standard maternal care) – at her second visit during pregnancy (8th week of gestation) advised her not to do any further testing. Everything would go well with the baby and the maternal age would not be that important until she would be 37 years old. B., however, who had already heard about the new blood test from friends and through the media, together with her 52-year-old partner decided to undergo NIPT. In Germany, NIPT is not generally covered by statutory health insurances yet (expected soon to be covered), so they would have to pay for it by themselves. She received no further counselling related to NIPT from her gynecologist, but he agreed to take the blood sample in the 11th week of pregnancy and to send it to an US provider, although he did not support this idea from his professional point of view and had no experience with the test procedure, too. When she came for her third visit in the 11th week, he had forgotten to arrange everything for the test, so that she had to wait another week and then came back. When the blood sample was taken, she was in the 12th week of pregnancy. A long time of waiting followed: after two weeks, when results should have been available at the latest, B. asked for results, but was told by the doctor’s receptionist that they had received nothing so far and that she had to wait longer. During the following days and weeks B. repeated her inquiries, but still got no information about any results. In the 18th week of gestation, the physician finally called her to let her know that the blood sample obviously had been lost in the US (according to his account). He advised her to check the bank account in order to see if any costs for the test had been debited (which had not).

She then, together with her partner and again without any further counselling, opted for a special ultrasound scan for fetal anomalies in her 20th week of gestation and thus arranged an appointment with a prenatal diagnostics specialist by herself. At her next regular visit in the 19th week, her gynecologist suspected a cardiac anomaly of the fetus during ultrasound scan. With regard to the consequences of this finding he told B., who wanted to have a home birth, that she should not worry – birth just would have to take place in a hospital now. At that time he recommended to see a specialist for prenatal ultrasound in order to further evaluate his findings.

The special ultrasound scan revealed multiple and severe malformations of the fetus in e.g. the heart, brain and face. Immediately, a chorionic villus sampling and an amniocentesis had been performed and both confirmed the result of a trisomy 13 in the fetus. Now B. was in her 20th week – a medical induction of labour was her only option at this point if she wanted to terminate pregnancy. The sudden shock of the result without any warning signs before, together with the following late termination of pregnancy inevitably caused a trauma.

Discussion

Several insufficiencies in the medical and counselling process are obvious in this case. For a deeper understanding we focus on two levels: individual failure as well as the structural, regulative setting. On the individual level this case illustrates impressively how influential personal attitudes and knowledge of clinicians in prenatal testing are. Apart from NIPT, physicians must be aware of their individual skills and honestly scrutinize their attitudes towards prenatal testing in order to enable autonomous reproductive choices. There is a broad agreement – not only in the opinions and statements mentioned above – that NIPT in practice needs a profound pre- and post-test counselling [10, 11]. B.’s gynecologist from the beginning did not hide his personal aversion towards advanced prenatal testing. Furthermore, he had not the additional, legally required training for offering NIPT and no practical experience with the test at all. In this constellation, adequate pre-test counselling is hardly possible and the resulting shared decision making (SDM) can only be deficient. While a physician’s personal aversion to NIPT of course is a general problem for the decision making process, the lacking knowledge leads to a concrete deficit: information sharing, one of SDM main pillars, cannot be conducted. It would have been the physician’s liability in this case to recognize his lack in knowledge as a potential risk, not only for the SDM. He then should have recommended that B. should see a colleague with more specific expertise.

As B. told us, one main reason for her to do the blood test was being able to terminate at an early gestational age in case of a serious disorder in the fetus. With his skeptical attitude towards prenatal testing, the lacking knowledge about NIPT and the resulting inactivity in his interaction with B. and the provider, the physician therefore ultimately restricted B.’s reproductive autonomy.

Since this case was not persecuted legally, we are finally not able to clarify what happened to the blood sample. The situation for German physicians regarding liability aspects has been improved since NIPT’s market launch in 2012: Lifecodex (“PraenaTest”) and Ariosa (“Harmony”) laboratories analyse blood samples in Germany CE-certified, Natera (“PraenaTest”) still in the United States, the German provider declares to take liability risks. However, the solution of liability questions of course does not guarantee an absence of process- and communication related risks, especially for unexperienced providers. Besides, B.’s case had been discovered accidentally during our search for pregnant women as interview partners for our research. This leads us to assume a larger estimated number of unreported cases of a failed NIPT usage, hopefully not many with similar consequences as reported here.

So, regarding this case of medical malpractice only as a physician’s individual failure, and therefore as an unfortunate exceptional event, would be shortsighted. Deficits in the regulative framework promote such potential misconduct and must be taken into consideration as well. The problem here is that regulations not only need to be improved and adjusted with regard to the new NIPT technologies. At least in Germany they have already shown to be insufficient for the regulation of established procedures of prenatal (genetic) diagnosis at all. Many well-known ethical difficulties and practical problems now simply are transferred to the new technology. It is no secret that there is often a gap between legal framework requirements such as from the GenDG and actual consultations. This gap could be re-
duced, for example, by sharpening the counselling requirements for gynecologists in prenatal testing together with an improve-ment of the existing advanced trainings. Basic requirements should become more standardized in order to ensure sufficient skills levels. At this point, the professional organisations bear re sponsibility for their members’ qualification status in order to be less volatile than today.

Structural safeguards in prenatal care with regard to necessary professional skills are indispensable, if cases as described above shall be prevented henceforth. Thus, it is not enough to limit the provision of NIPT to MFM specialists. The question here is not only who now should be allowed to provide NIPT [12]. In one study several clinicians and also MFM specialists (13%) declared to offer NIPT as a diagnostic test [9]. Another study showed 6% of women terminating pregnancy without karyotype confirmation after getting pathological findings from NIPT [5]. Therefore it has to be ensured effectively that the providing clinician has a sufficient training in prenatal care counselling which allows her to reflect upon and professionally dissociate herself from own personal attitudes towards prenatal testing. Again, professional organisations have to make sure that physicians are well informed and, thus, are able to inform women thoroughly in turn.

More NIPT specific questions include: Is there a sufficient failure management on the commercial providers’ side? The significant difference between shipping a blood sample thousands of miles for doing a genetic testing and an on-site blood test result must be internalized by all agents involved. There should be standard ized procedures in the prenatal care pathway for occurring process-related problems in order to minimize time loss – little delay might not be an obvious risk for providers and physicians but in total can become essential for the pregnant woman as the reported case shows.

Furthermore, it can be argued that NIPT at least in the short run should not replace the first-trimester screening (FTS), although it has significantly lower false-positive rates and a significantly higher positive predictive value [13, 14]. As long as NIPT is not implemented together with an adequate quality management, a parallel testing procedure even can be seen as a clinical utility. In B.’s case NIPT alone, if performed accurately, most likely would have shown a trisomy 13. A FTS would have shown signs of variation as well. Since NIPT for trisomy is superior to the combined test, the role of high-quality first-trimester ultrasound scan should be emphasized [15]. Still too expensive for most pregnant women, NIPT with its limited diagnostic scope should be seen as an additional screening test rather than an alternative to high-quality ultrasound-scan, which is able to detect a much wider range of potential anomalies. This is an important difference that should be communicated more clearly – to pregnant women as well as within the professional community. With a combination of both non-invasive testing procedures, process-related vulner abilities of each procedure could be moderated more effectively. Returning to B.’s case, a well performed FTS ultrasound scan could have compensated the time loss caused by the failed NIPT usage. Many questions of how to include NIPT responsibly into every day practice have not been answered adequately yet in many countries and become more urgent in light of the forthcoming coverage by health insurances and increasing numbers of tests. Clinicians report insecurities with regard to the adequate provision of NIPT services and ask for specific legal regulations [10], as also expert interviews from our project confirm (unpublished data). If cases like the reported example shall be avoided in the future, it is inevitable to install effective safeguards for the shared decision making process in prenatal testing against individual and structural inadequacies related to the increasing use and sig nificance of NIPT.

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Conflict of Interest

None.

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