ISSN: 2536-7153 SJMLS

Sokoto Journal of Medical Laboratory Science 2024; 9(4): 169 - 180

SJMLS - 9(4) - 019

# Current Approaches to Prenatal Diagnosis of Sickle Cell Anaemia

Ibrahim Kalle Kwaifa*, and Ismail Usman Adekunle
Department of Haematology, School of Medical Laboratory Sciences, College of Health Sciences, Usmanu Danfodiyo University (UDU), Sokoto, North-Western, 2346, Nigeria

Author for Correspondence: Ibrahim.kwaifa@udusok.edu.ng/+234-703-548-394
https://dx.doi.org/10.4314/sokjmls.v9i4.19

**Summary**
Sickle Cell Anaemia (SCA) is an inherited disease characterized by production of an abnormal haemoglobin, leading to significant health conditions and reduction in patients' quality of life. Globally, the World Health Organization (WHO) reports that 300,000-400,000 new-borns are born with SCA annually. It is an inherited as a recessive trait, which presents a major health challenge, particularly in areas with high incidence rates. Prenatal screening for SCA play a very vital role as it enables early interventions, allows for informed choices on pregnancy management, and guides family decision-making. Accurate diagnosis enables parents to make potential interventions, and future family planning. Advanced testing methods have made SCA diagnosis more accurate and less invasive for earlier detection. The aim of this study was to provide an in-depth analysis of the current state of prenatal diagnosis for SCA. Data were generated from PubMed, Google Scholar, Tailor and Francis, MDPI, Springer, Nature, BMC and some other related information. By examining the advantages, limitations, and accuracy of these methods. In conclusion, the future of prenatal testing for Sickle Cell Anaemia is poised for revolutionary advancements. NIPT emerges as the most promising approach, offering; earlier detection, as early as 5-6 weeks' gestation, higher accuracy and sensitivity, enhanced safety and increased accessibility and affordability. As NIPT continues to advance, integrating artificial intelligence, epigenetic markers, and CRISPR-based diagnostics, it will become the gold standard for Sickle Cell Anaemia diagnosis. Embracing NIPT and its future developments will empower precise and compassionate care, transforming the lives of individuals and families affected by Sickle Cell Anaemia.

**Keywords:** Sickle cells anaemia, current prenatal diagnosis and future perspective

## 1.0 Introduction

Sickle Cell Anaemia (SCA) is a genetic condition that disrupts haemoglobin production, leading to serious health issues and lowering patients' quality of life (Hoseini *et al.,* 2020). The disease, which is inherited as a recessive trait, presents a major health challenge, especially in regions with high prevalence rates (WHO, 2020). Prenatal testing for SCA is essential as it enables early interventions, guides family decision-making, and allows for informed choices on pregnancy management. Accurate diagnosis enables parents to make informed choices regarding pregnancy management, potential interventions, and future family planning (Dhoda *et al.,* 2019). Recent improvements in testing methods have made SCA diagnosis more accurate and less invasive, allowing for earlier detection (Bereir *et al.,* 2022). By examining the advantages, limitations, and accuracy of these methods, this study aims to provide an in-depth analysis of the current state of prenatal diagnosis for SCA. This review provides details information on the current diagnostic methods for SCA, their benefits, limitations, and accuracy, as well as ethical issues, counselling methods, and future directions in SCA prenatal testing (Bereir *et al.,* 2022).

### 1.2 Epidemiology of Sickle Cell Anaemia

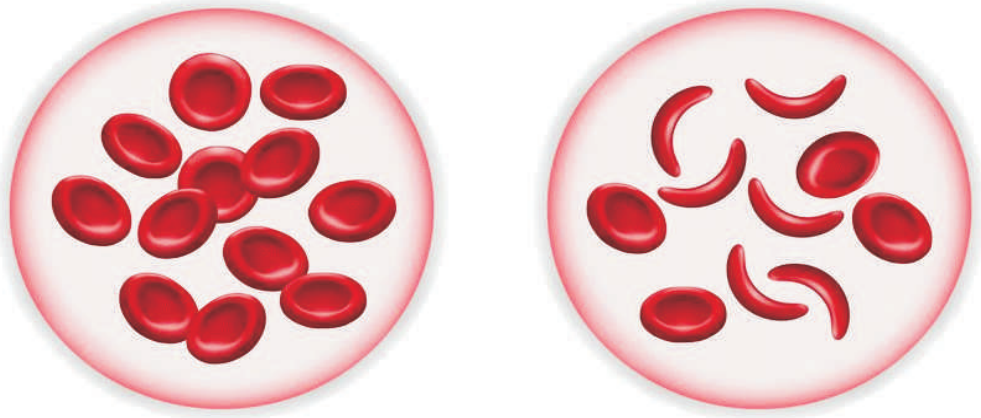
Sickle cell anaemia (SCA) is a widespread health issue impacting large populations worldwide. According to recent estimates, in the United States, approximately 100,000 people are affected by SCA (Hood *et al.,* 2020). The highest prevalence of SCA is found in sub-Saharan Africa, where it affects 1-2% of births (Grosse *et al.,* 2011). These regions bear the largest burden of SCA, with countries, including Nigeria, the Democratic Republic of Congo, and Ghana having the highest numbers of affected individuals. These statistics highlight the need for increased awareness, improved access to diagnosis and treatment, and enhanced healthcare infrastructure to support individuals living with SCA.

The incidence of sickle cell anaemia (SCA) varies by ethnicity and geographic location. In the United States; Approximately 1 in 500 African American births are affected by SCA (Hood *et al.,* 2020). About1 in 1,000-1,400 Hispanic American births are affected by SCA (Hood *et al.,* 2020). While about 1 in 2,000-2,500 Caucasian American births are affected by SCA (Hood *et al.,* 2020). Globally, the incidence of SCA is highest in regions with high frequencies of the sickle cell trait, including Sub-Saharan Africa: 1-2% of births (Grosse *et al.,* 2011), Mediterranean region: 1-5% of births (WHO, 2020), Middle East and South Asia: 1-3% of births (WHO, 2020). Understanding the epidemiology of SCA is crucial for developing targeted public health initiatives, genetic counselling programs, and new-borns screening strategies.

Sickle cell anaemia (SCA) is the leading cause of morbidity and mortality worldwide, particularly in low- and middle-income countries. The mortality rate for SCA is significant, accounting for 50-90% of sickle cell disease-related deaths (Platt *et al.,* 2018), while early childhood mortality ranges from 20-30% in Africa (Grosse *et al.,* 2011). High mortality rates are in low-income countries due to limited access to healthcare, diagnostic facilities, and treatment options (WHO, 2020). In the United States, advances in medical care have reduced mortality rates, but SCA remains a significant cause of premature death, especially among young adults (Hood *et al.,* 2020).

### 1.3 Genetics and Inheritance Patterns

SCA is caused by a mutation in the haemoglobin-beta gene, leading to the production of haemoglobin S (HbS), which results in misshapen, "sickled" red blood cells. Grasping the genetics and inheritance patterns of Sickle Cell Anaemia (SCA) is crucial for effective diagnosis, patient counselling, and disease management. Haemoglobin, a protein found in red blood cells, plays a key role in carrying oxygen from the lungs to body tissues and transporting carbon dioxide back to the lungs. Normal haemoglobin (HbA) is made up of two alpha (2α) and two beta (2β) globin chains (Bunn and Forget, 2017). The HBB gene, located on chromosome 11, is responsible for producing the beta globin chain (Thein and Menzel, 2009). Sickle cell anaemia arises from a single base substitution (adenine to thymine) in the sixth codon of the HBB gene, which changes glutamic acid to Valine in the beta globin chain (Higgs *et al.,* 2012). This mutation leads to the formation of haemoglobin S (HbS), which clumps together under low oxygen levels, causing red blood cells to take a sickle shape (Fig. 1) (Rees, Williams, and Gladwin, 2010).



**Normal red blood cells** **Sickled red blood cells**

**Figure 1: Normal and Sickle Red Blood Cells (NIH, 2022).**

Sickle Cell Anaemia (SCA) is passed down through an autosomal recessive inheritance pattern, meaning an individual needs to receive two copies of the sickle cell gene, one from each parent to develop the disease (Thein and Menzel, 2009). The inheritance patterns can be described as follows:

1. ***Homozygous (HbSS):*** Individuals with two HbS alleles (HbSS) have sickle cell anaemia, showing the full range of symptoms, such as pain episodes, anaemia, and organ damage (Higgs *et al*, 2012).

2. ***Heterozygous (HbAS):*** People with one HbS allele and one normal allele (HbAS) carry the sickle cell trait. These individuals typically do not show symptoms but can pass the HbS allele to their children (Naik and Haynes, 2018). The sickle cell trait also offers some protection against malaria, explaining its higher frequency in areas where malaria is common (Rees *et al.,* 2010).

3. ***Compound Heterozygous***: Some individuals inherit one HbS allele along with another variation of the beta globin gene, such as haemoglobin C (HbSC) or beta-thalassemia (HbS/β-thal). These compound heterozygous forms can lead to a range of clinical severity (Higgs *et al.,* 2012). The risk of passing on SCA depends on the genetic status of the parents:

***Two Carriers (HbAS x HbAS):*** When both parents are carriers of the sickle cell trait (HbAS), each child has a 25% probability of having Sickle Cell Anaemia (HbSS), a 50% chance of being a carrier (HbAS), and a 25% chance of inheriting normal haemoglobin (HbAA) (Fig. 2) (Higgs *et al.,* 2009).

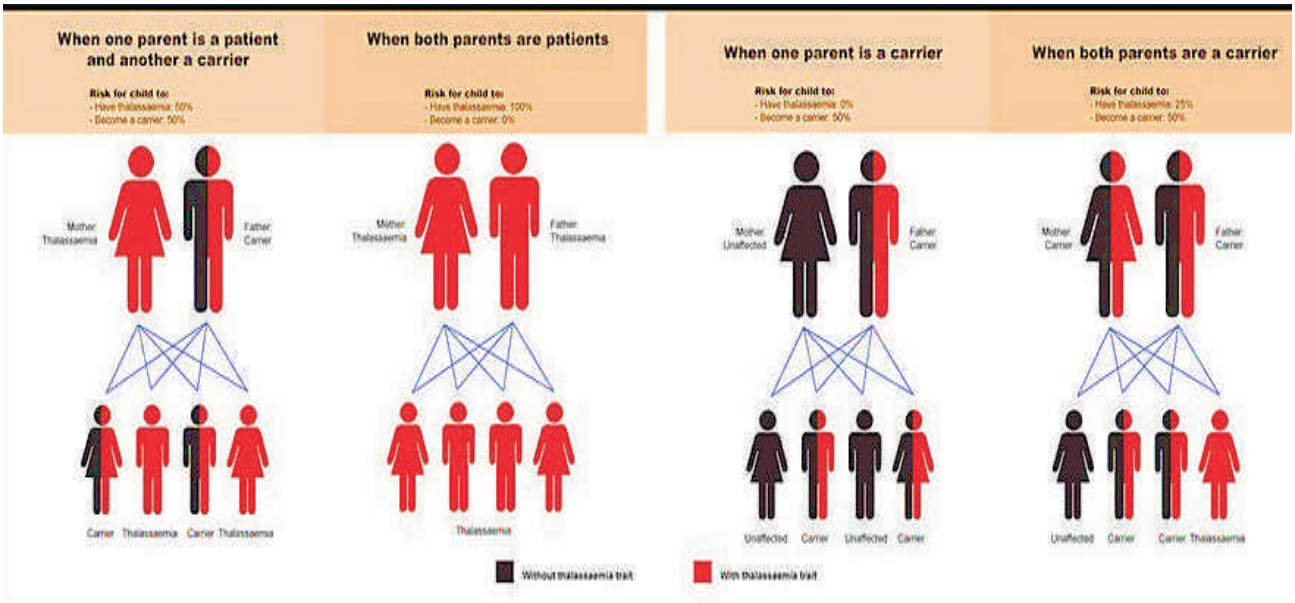



**Figure 2: Inheritance Pattern Sickle Cell Anaemia** (Higgs *et al.,* 2009).

***Carrier and Affected (HbAS x HbSS)****:* When one parent is a carrier (HbAS) and the other has Sickle Cell Anaemia (HbSS), each child has a 50% chance of inheriting Sickle Cell Anaemia (HbSS) and a 50% chance of being a carrier (HbAS) (Fig. 3) (Naik and Haynes, 2018).

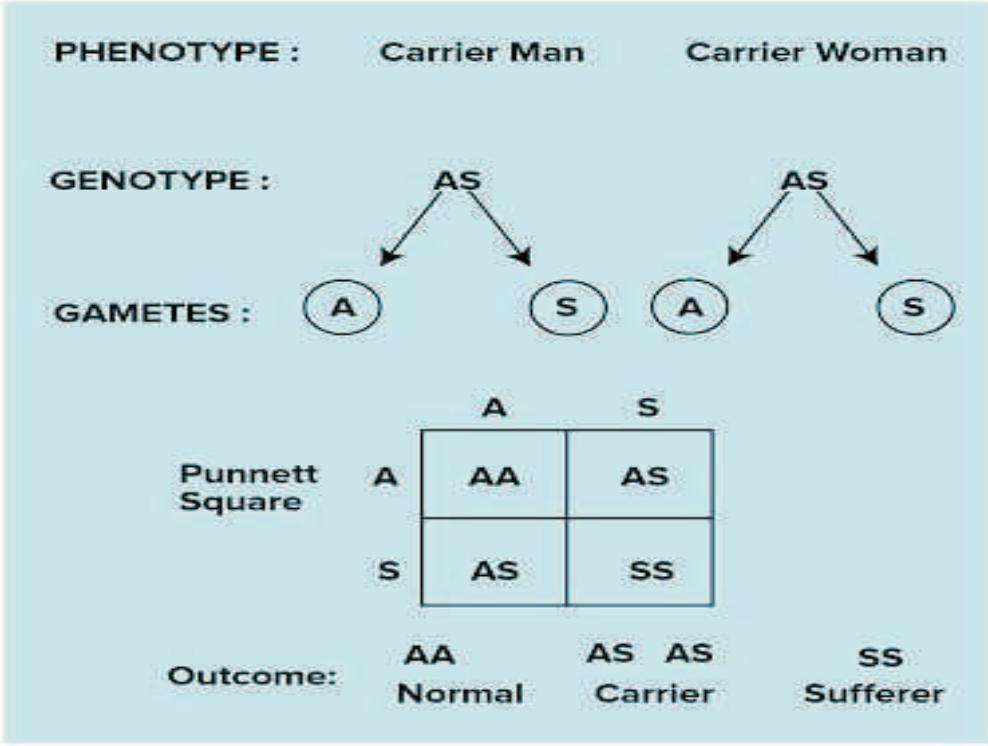
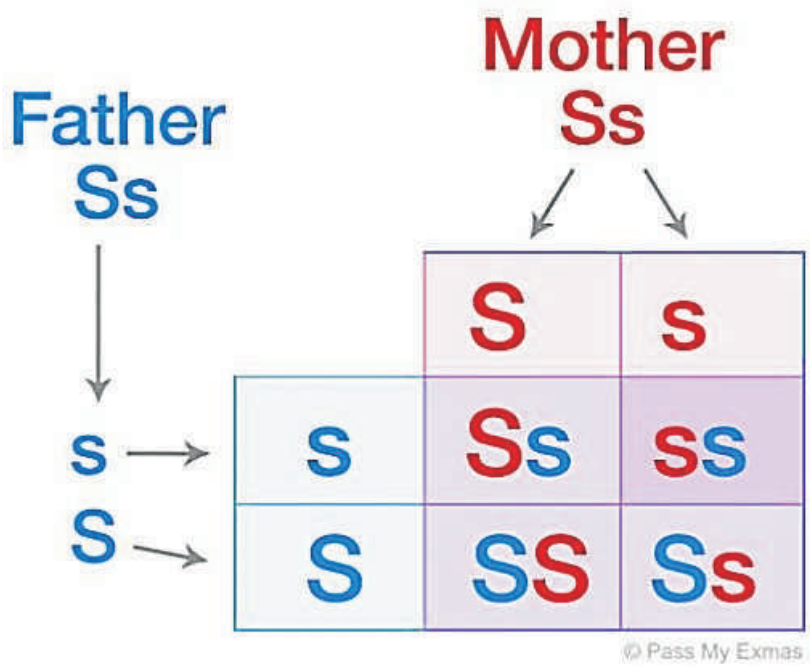



**Figure 3: Inheritance pattern for carrier and affected** (Naik and Haynes, 2018).

***Two Affected (HbSS x HbSS):*** Each child will have SCA (HbSS) (Fig. 4) (Higgs *et al.,* 2009).




**Outcome: SS= Sufferer**
**Figure 4: Inheritance Pattern for two Carriers** (Higgs *et al.,* 2009).

## 2.0 Importance of Prenatal Diagnosis of Sickle Cell Anaemia

Prenatal diagnosis of sickle cell anaemia (SCA) is crucial for several reasons:

1. Genetic Counselling: Prenatal testing offers a chance for genetic counselling, helping families comprehend the risks and potential outcomes of Sickle Cell Anaemia (SCA) (American College of Obstetricians and Gynaecologists, 2020a).
2. Early Intervention: Detecting SCA before birth allows for early intervention, such as specialized prenatal care and planning for managing the condition after birth (Hassell, 2019).
3. Family Planning: Prenatal testing provides essential information that aids families in making informed choices about family planning and reproduction (Kuliev *et al.,* 2019).
4. Psychological Preparation: Knowing about SCA in advance allows parents to emotionally and mentally prepare for raising a child with a chronic illness (Hood *et al.,* 2020).
5. Reduced Morbidity and Mortality: Early diagnosis and intervention can lower the risk of complications and death associated with SCA (Platt *et al.,* 2018).
6. Reduced Healthcare Costs: Early management of SCA can help reduce the medical costs linked to the condition (Hood *et al.,* 2020).
7. Improved Outcomes: Prenatal diagnosis and timely care improve the long-term health and quality of life for individuals with SCA (Grosse *et al.,* 2011).
8. Access to Specialized Care: Prenatal diagnosis ensures that families have access to specialized care centre and treatment resources for SCA (Bianchi *et al.,* 2020).
9. Increased Awareness: Prenatal testing raises awareness about SCA, encouraging education and advocacy effort (Kuliev *et al.,* 2019).
10. Informed Decision-Making: Prenatal testing enables parents to make informed choices regarding their pregnancy, including decisions about whether to continue or terminate it (American College of Obstetricians and Gynaecologists, 2020b).

By highlighting the importance of prenatal diagnosis, we can emphasize the need for accessible and accurate testing, ensuring that families receive the support and care they need.

## 2.1 Methods of Prenatal Diagnosis of Sickle Cell Anaemia

There are three main methods of prenatal diagnosis of sickle cell anaemia, which are:

1. Chorionic Villus Sampling (CVS)
2. Amniocentesis
3. Non-Invasive Prenatal Testing (NIPT, 2020).

### 2.1.1 Chorionic Villus Sampling (CVS)

Chorionic Villus Sampling (CVS) is a prenatal test that involves collecting a small sample of placental cells, known as chorionic villi, to identify genetic disorders and chromosomal abnormalities (Hobbins, 2018). This test is typically conducted between 10 and 12 weeks of pregnancy (Hobbins, 2018). CVS is generally offered only when there is a high likelihood that the baby may have a genetic or chromosomal condition (American College of Obstetricians and Gynaecologists, 2020c).

There are two methods:

1. Transcervical CVS: A catheter is inserted through the cervix and directed to the placenta with ultrasound guidance.
2. Transabdominal CVS: A needle is inserted through the abdomen and guided to the placenta with ultrasound assistance (Fig. 5) (American College of Obstetricians and Gynaecologists, 2020c).

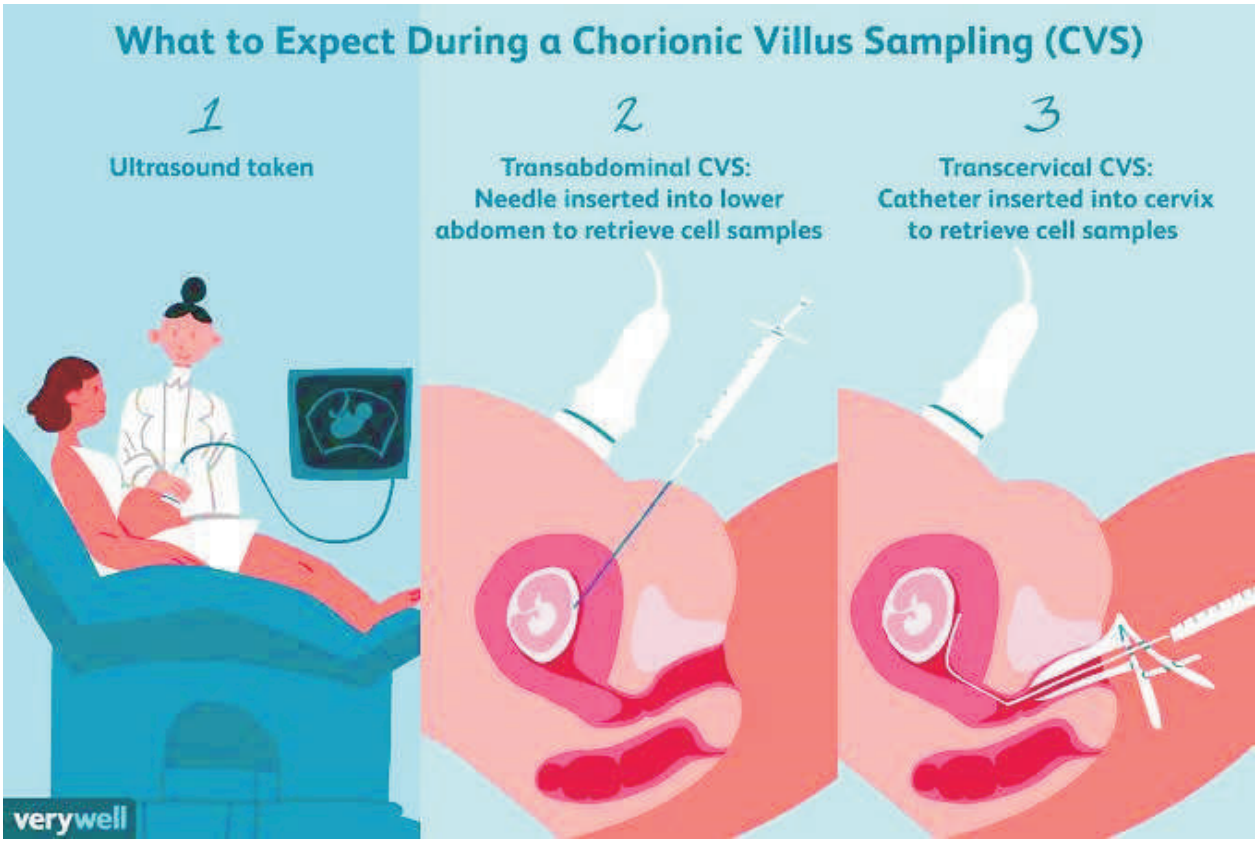



**Figure 5: Transabdominal and Transcervical CVS** (American College of Obstetricians and Gynaecologists, 2020).

**Procedure**

***Step 1: Preparation*:** Before starting, an ultrasound is performed to verify the gestational age and locate the placenta. The woman lies on her back with her abdomen exposed, which is then cleaned and prepared for the procedure (American College of Obstetricians and Gynaecologists, 2020b).

***Step 2: Ultrasound Guidance***: The healthcare provider uses ultrasound to guide the procedure, helping to identify the precise location of the placenta and the best spot for sampling (Hobbins, 2018).

***Step 3: Insertion of the Catheter or Needle***: For transcervical CVS, a catheter is inserted through the cervix and directed to the placenta (Hobbins, 2018). In transabdominal CVS, a needle is inserted through the abdomen to reach the placenta (American College of Obstetricians and Gynaecologists, 2020a).

***Step 4: Sampling:*** Once in position, a small sample of chorionic villi is collected and sent to the laboratory for analysis (Kuliev *et al.,* 2019). The sampling process takes about 10 minutes, while the entire appointment may last around 30 minutes (Hobbins, 2018).

***Step 5: Post-Procedure Care:*** After the procedure, the woman is observed for any possible complications or side effects. Some mild cramping, bleeding, or spotting may occur, but these effects are usually temporary (Kuliev *et al.,* 2019).

**Advantages**

***Early diagnosis:*** CVS can diagnose genetic disorders and chromosomal abnormalities earlier than amniocentesis (15-20 weeks) (Hobbins, 2018).

***Accurate results:*** CVS has a high accuracy rate (over 99%) for detecting chromosomal abnormalities (Kuliev *et al.,* 2019).

***Reduced risk of miscarriage:*** CVS has a lower risk of miscarriage compared to amniocentesis (American College of Obstetricians and Gynaecologists, 2020b).

**Limitations**

***Miscarriage:*** CVS carries a small risk of miscarriage (less than 1%) (Hobbins, 2018).

***Infection:*** As with any invasive procedure, there is a risk of infection (American College of Obstetricians and Gynaecologists, 2020c).

***Bleeding:*** Some women may experience bleeding or spotting after CVS (Kuliev *et al.,* 2019).

**2.1.2 Amniocentesis**

Amniocentesis is a prenatal diagnostic procedure that involves withdrawing a sample of amniotic fluid from the uterus to test for various genetic and chromosomal abnormalities in the foetus (American College of Obstetricians and Gynaecologists, 2020). The procedure is typically performed between 15 and 20 weeks of gestation, although it can be done as early as 11 weeks (Fig. 6) (National Institute of Child Health and Human Development, 2022).

***Amniocentesis can detect various conditions, including:***

- Chromosomal abnormalities, such as Down syndrome (trisomy 21) and trisomy 18 (National Down Syndrome Congress, 2022)
- Genetic disorders, such as cystic fibrosis and sickle cell disease (Genetic Alliance, 2022)
- Neural tube defects, such as spina bifida (Spina Bifida Association, 2022)

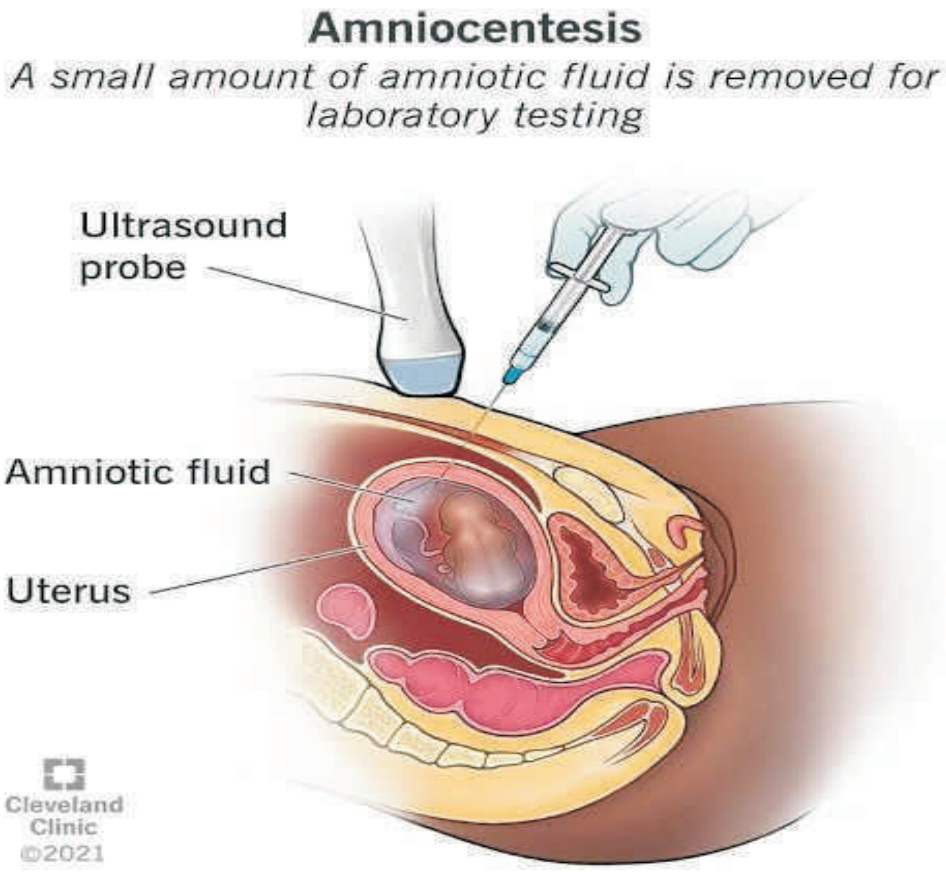



**Figure 6: Procedure for collecting Amniotic fluid** (American College of Obstetricians and Gynaecologists, 2020a).

**Procedure**

***Step 1: Preparation***: The patient is asked to lie on their back and expose their abdomen. The healthcare provider cleans and prepares the abdomen with antiseptic solution (American College of Obstetricians and Gynaecologists, 2020b).

***Step 2: Ultrasound Guidance:*** An ultrasound machine is used to visualize the foetus and the amniotic fluid sac. This helps the healthcare provider to determine the best location for inserting the needle (Society for Maternal-Foetal Medicine, 2020).

***Step 3: Insertion of the Needle:*** A thin needle (usually 20-22 gauge) is inserted through the abdomen and into the uterus, guided by ultrasound imaging. The needle is inserted to a depth of about 1-2 inches (National Institute of Child Health and Human Development, 2022).

***Step 4: Withdrawal of Amniotic Fluid:*** A syringe is attached to the needle, and a sample of amniotic fluid (usually 10-20 mL) is withdrawn. The fluid is clear or pale yellow in colour. (American Pregnancy Association, 2022).

***Step 5: Removal of the Needle***: The needle is removed from the abdomen, and the puncture site is cleaned and dressed with a bandage (Society for Maternal-Foetal Medicine, 2020).

***Step 6: Analysis of the Sample:*** The amniotic fluid sample is sent to a laboratory for analysis, which may include chromosomal analysis (karyotyping), genetic testing (e.g., DNA analysis) and biochemical testing (e.g., alpha-fetoprotein levels)

**Advantages:**

1. ***Accurate diagnosis***: Amniocentesis can accurately diagnose chromosomal abnormalities, such as Down syndrome, trisomy 18, and trisomy 13, as well as genetic disorders like cystic fibrosis and sickle cell disease (American College of Obstetricians and Gynaecologists, 2020b).
2. ***Early detection:*** Amniocentesis can detect abnormalities early in pregnancy, allowing for timely decision-making and planning. This can be especially important for women who are at high risk for genetic disorders or have a family history of certain conditions (National Institute of Child Health and Human Development, 2022).
3. ***Reduced uncertainty***: Amniocentesis can provide reassurance for women with a high-risk pregnancy or family history of genetic disorders. A normal test result can reduce anxiety and uncertainty, allowing women to focus on a healthy pregnancy (Society for Maternal-Foetal Medicine, 2020).
4. ***Informed decision-making***: Amniocentesis allows women to make informed decisions about their pregnancy, including whether to continue or terminate. This can be especially important for women who are at high risk for genetic disorders or have a family history of certain conditions (American Pregnancy Association, 2022).

**Limitations:**

***Risk of miscarriage***: Amniocentesis carries a small risk of miscarriage, estimated to be less than 1%. This is estimated to occur in up to 1 out of every 200 women who have amniocentesis. This risk is higher for women who have a history of miscarriage or cervical insufficiency (American College of Obstetricians and Gynaecologists, 2020a).

***Infection risk:*** Amniocentesis carries a small risk of infection, estimated to be less than 1%. This risk can be minimized with proper technique and sterile equipment (National Institute of Child Health and Human Development, 2022).

***Foetal injury risk:*** Amniocentesis carries a small risk of foetal injury, estimated to be rare. This risk can be minimized with proper technique and ultrasound guidance (Society for Maternal-Foetal Medicine, 2020).

***Limited scope:*** Amniocentesis only tests for specific conditions and may not detect all genetic disorders or abnormalities. Additional testing, such as chorionic villus sampling (CVS), may be necessary for a comprehensive diagnosis (American Pregnancy Association, 2022).

***Timing limitations:*** Amniocentesis is typically performed between 15 and 20 weeks of

gestation, which may be too late for some women to make decisions about their pregnancy (National Institute of Child Health and Human Development, 2022).

### 2.1.3 Non-Invasive Prenatal Testing (NIPT)

Non-Invasive Prenatal Testing (NIPT) is a diagnostic method that analyses cell-free DNA (cfDNA) from the mother's blood to detect genetic disorders in the foetus. This test is non-invasive, meaning it doesn't require any needles or procedures that could harm the mother or foetus (Fig. 7) (Bianchi *et al.,* 2014).

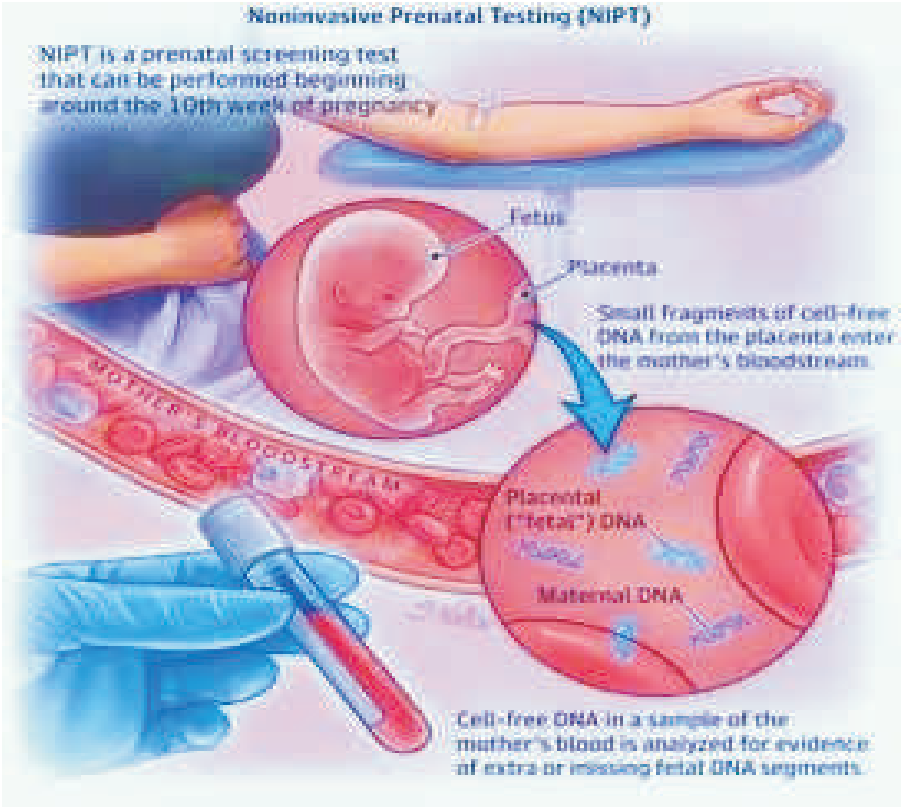



**Figure 7: Non-invasive Prenatal Testing Procedure (Harraway, 2017).**

NIPT can detect sickle cell anaemia by identifying the presence of the HBB gene mutation (HbS) in the foetal DNA. This is done by:

1. Analysing the cfDNA for the HbS mutation: The cfDNA is analysed for the presence of the HbS mutation.
2. Determining the percentage of HbS alleles: The percentage of HbS alleles in the cfDNA is determined.
3. Comparing the results to a threshold value: The results are compared to a threshold value to determine the risk of sickle cell anaemia (Bianchi *et al.,* 2014).

**Procedure**

***Step 1: Blood Draw:*** A healthcare provider takes a sample of the mother's blood (typically 10-20 mL) from a vein in the arm. The blood is collected in a special tube containing an anticoagulant to prevent clotting (Bianchi *et al.,* 2014).

***Step 2: Plasma Separation:*** The blood sample is centrifuged to separate the plasma (the liquid portion) from the blood cells. The plasma is transferred to a new tube for further processing (Wapner *et al.,* 2012)

***Step 3: Cell-Free DNA (cfDNA) Isolation:*** The plasma is processed to isolate the cfDNA using specialized kits or reagents. The cfDNA is then extracted and purified using various methods (e.g., magnetic beads, columns) (Bianchi *et al.,* 2014).

***Step 4: Library Preparation:*** The isolated cfDNA is prepared for sequencing by creating a "library" of DNA fragments. This involves adding adapters, amplifying the DNA, and fragmenting it into smaller pieces (Wapner *et al.,* 2012).

***Step 5: Sequencing:*** The prepared library is then sequenced using Next-Generation Sequencing (NGS) technologies (e.g. Illumina, Ion Torrent). The sequencing generates millions of short DNA reads that are analysed to detect genetic variations (Bianchi *et al.,* 2014).

***Step 6: Data Analysis:*** The sequencing data is analysed using specialized software to detect the presence of the HBB gene mutation (HbS) associated with sickle cell anaemia. The analysis involves comparing the foetal DNA sequences to a reference genome and identifying any variations (Wapner *et al.,* 2012).

***Step 7: Results Interpretation:*** The results are interpreted by a healthcare provider or genetic counsellor to determine the risk of sickle cell anaemia. A positive result indicates the presence of the HbS mutation, while a negative result indicates the absence of the mutation (Bianchi *et al.,* 2014).

***Step 8: Confirmation Testing (if necessary):*** If the NIPT result is positive, confirmatory testing (e.g., CVS, amniocentesis) may be recommended to confirm the diagnosis (Wapner *et al.,* 2012).

**Advantages**

NIPT offers several advantages, including:

1. *Non-invasive and safe*: NIPT is non invasive and safe for the mother and foetus.
2. ***Early detection:*** NIPT can detect sickle cell anaemia as early as 9-10 weeks of gestation.
3. ***High accuracy:*** NIPT has a high accuracy (>99%) for detecting sickle cell anaemia.
4. ***Reduced need for invasive testing***: NIPT reduces the need for invasive testing (CVS or amniocentesis) (Gregg *et al.,* 2016).

**Limitations**

***False positives and false negatives can occur:*** False positives and false negatives can occur due to various factors, such as maternal DNA contamination or limited DNA sequencing.

***Limited ability to detect other genetic conditions:*** NIPT is primarily designed to detect sickle cell anaemia and other common aneuploidies. It may not detect other genetic conditions (Bianchi *et al.,* 2014).

**Future Perspectives**

***Artificial intelligence integration:*** Enhanced data analysis and pattern recognition.

***Epigenetic marker development:*** New biomarkers for improved SCA detection.

***CRISPR-based diagnostics:*** Potential for rapid, accurate, and cost-effective testing.

***Global accessibility:*** Expansion of testing services, particularly in resource-limited settings, making testing more affordable and widespread.

***Personalized medicine approaches***: Tailored genetic counselling, management, and treatment.

***Point-of-care testing will become a reality, enabling rapid bedside testing.***

These future prospects aim to enhance the accuracy, safety, and accessibility of prenatal testing for Sickle Cell Anaemia, revolutionizing diagnosis and management.

These advancements will revolutionize Sickle Cell Anaemia diagnosis, enabling:

- Earlier intervention and management
- Improved patient outcomes
- Enhanced personalized care
- Increased accessibility and affordability
- Better understanding and treatment of SCA

The future of prenatal testing holds immense promise, transforming the lives of individuals and families affected by Sickle Cell Anaemia.

**Conclusion**

In conclusion, the future of prenatal testing for Sickle Cell Anaemia is poised for revolutionary advancements. NIPT emerges as the most promising approach, offering; earlier detection, as early as 5-6 weeks' gestation, higher accuracy and sensitivity, enhanced safety and increased accessibility and affordability. As NIPT continues to advance, integrating artificial

intelligence, epigenetic markers, and CRISPR-based diagnostics, it will become the gold standard for Sickle Cell Anaemia diagnosis. Embracing NIPT and its future developments will empower precise and compassionate care, transforming the lives of individuals and families affected by Sickle Cell Anaemia.

**Acknowledgement**: I would like to sincerely appreciate all the authors who contributed financially to the payment of the article processing fee for this manuscript. I would also especially like to thank all the authors for their constant support, direction, and encouragement.

**Conflict of interest:** All authors declare that they have no competing interests.

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**Citation:** Ibrahim Kalle Kwaifa, and Ismail Usman Adekunle. Current Approaches to Prenatal Diagnosis of Sickle Cell Anaemia. ***Sokoto Journal of Medical Laboratory Science*; 9(4): 169 – 180**
https://dx.doi.org/10.4314/sokjmls.v9i4.19