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ORIGINAL ARTICLE

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Impact of high-risk prenatal screening results for 22q11.2 deletion syndrome on obstetric and neonatal management: Secondary analysis from the SMART study

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Abstract

Objective: One goal of prenatal genetic screening is to optimize perinatal care and improve infant outcomes. We sought to determine whether high-risk cfDNA screening for 22q11.2 deletion syndrome (22q11.2DS) affected prenatal or neonatal management.

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Methods: This was a secondary analysis from the SMART study. Patients with high-risk cfDNA results for 22q11.2DS were compared with the low-risk cohort for pregnancy characteristics and obstetrical management. To assess differences in neonatal care, we compared high-risk neonates without prenatal genetic confirmation with a 1:1 matched low-risk cohort.

Results: Of 18,020 eligible participants enrolled between 2015 and 2019, 38 (0.21%) were high-risk and 17,982 (99.79%) were low-risk for 22q11.2DS by cfDNA screening. High-risk participants had more prenatal diagnostic testing (55.3%; 21/38 vs. 2.0%; 352/17,982, $p < 0.001$) and fetal echocardiography (76.9%; 10/13 vs. 19.6%; 10/51, $p < 0.001$). High-risk newborns without prenatal diagnostic testing had higher rates of neonatal genetic testing (46.2%; 6/13 vs. 0%; 0/51, $P < 0.001$), echocardiography (30.8%; 4/13 vs. 4.0%; 2/50, $p = 0.013$), evaluation of calcium levels (46.2%; 6/13 vs. 4.1%; 2/49, $P < 0.001$) and lymphocyte count (53.8%; 7/13 vs. 15.7%; 8/51, $p = 0.008$).

Conclusions: High-risk screening results for 22q11.2DS were associated with higher rates of prenatal and neonatal diagnostic genetic testing and other 22q11.2DS-specific evaluations. However, these interventions were not universally performed, and >50% of high-risk infants were discharged without genetic testing, representing possible missed opportunities to improve outcomes for affected individuals.

Key points

What is already known about this topic?

- The 22q11.2 deletion syndrome occurs in approximately 1 in 2000 pregnancies, unrelated to maternal age, with 5%–10% inherited from a parent.
- Although variability in the neurocognitive and structural phenotype exists, early interventions in the neonatal period are available to improve many outcomes.
- Prenatal cfDNA screening for 22q11.2DS has been demonstrated to have a high sensitivity (83%) and modest positive predictive value (52%).

What does this study add?

- Confirmatory genetic testing, as well as obstetrical and neonatal evaluation and interventions, are inconsistently performed after high-risk cfDNA screening results for 22q11.2DS
- Approximately half of the infants at risk for 22q11.2DS based on high-risk cfDNA screening results are discharged from the hospital without confirmatory genetic testing or evaluation for 22q11.2DS-related abnormalities.
- To optimize outcomes for individuals with 22q11.2DS, prenatal and neonatal evaluation after high-risk cfDNA screening for 22q11.2DS is needed.

1 | INTRODUCTION

The 22q11.2 deletion syndrome (22q11.2DS), also known as DiGeorge or velo-cardio-facial syndrome, occurs in approximately 1 in 2000 live births.[1,2] Most cases arise as a de novo abnormality unrelated to maternal age, while about 5%–10% are inherited from a parent.[3] There are more than 50 genes in the 22q11.2 critical region,[4] leading to a complex and variable phenotype that can include congenital heart defects, a compromised immune system, orofacial clefts, palatal insufficiency, developmental delay, and schizophrenia. In an era prior to prenatal screening and comprehensive testing, the average age of diagnosis of 22q11.2DS was 4.7 years[5]

Historically, 22q11.2DS has been suspected in the pre- and perinatal period when ultrasound abnormalities, particularly conotruncal cardiac anomalies, were identified, prompting prenatal or postnatal diagnostic testing. However, some 22q11.2DS affected fetuses and neonates do not present with a cardiac anomaly, reducing the sensitivity of prenatal ultrasound for the detection of

22q11.2DS. The performance of cell-free DNA (cfDNA) screening for 22q11.2DS has been reported in several obstetrical cohorts with high sensitivity and low false-positive rates.[6–9]

The SMART study enrolled over 20,000 women who had prenatal screening for 22q11.2DS using SNP-based cfDNA and who consented to confirmatory genetic testing of the infant.[6] This study cohort presented an opportunity to determine not only the performance of cfDNA screening but also to obtain information regarding the clinical utility of universal screening for this condition as defined by observed changes in pregnancy outcome or prenatal/neonatal care, specifically the performance of diagnostic genetic testing and evaluations for cardiac anomalies and other phenotypic differences associated with 22q11.2DS.[10–17]

2 | METHODS

This study was a secondary analysis from the SMART study, wherein the population of pregnant individuals receiving a high-risk cfDNA result for 22q11.2DS along with a matched low-risk cohort were included. Supplementary data collection was performed to assess the differences in obstetrical and neonatal care based on cfDNA results for 22q11.2DS. Patients receiving a high-risk cfDNA result for 22q11.2DS were compared with the full low-risk cohort for pregnancy characteristics and obstetrical management. To assess differences in neonatal care based on cfDNA results for 22q11.2DS, we compared the relevant high-risk cohort with a control low-risk cohort with the goal of 1:1 matching.

The performance of cfDNA screening, data collection protocols and testing methodology for 22q11.2DS used in the SMART study have been described in detail.[6] Briefly, SMART study participants who received SNP-based cfDNA results for 22q11.2DS and had confirmatory genetic testing were eligible for participation in this study. Those with a high-risk result for autosomal aneuploidy were excluded. A risk of ≥1% for 22q11.2DS based on cfDNA analysis was reported as high-risk. Chromosomal microarray analysis (CMA) was requested for all newborns, regardless of clinical prenatal diagnostic testing. If postnatal CMA was not available, results from clinical testing with prenatal or postnatal CMA, fluorescence in situ hybridization, bacterial artificial chromosomes (BACs)-on-beads or multiplex ligation-dependent probe amplification were used for genetic confirmation if available. A deletion of ≥0.5 Mb in the 22q11.2 low copy repeat A-D region on diagnostic confirmatory testing was considered a positive test result. If the SMART study research CMA analysis identified a 22q11.2 deletion, and prenatal or postnatal confirmatory genetic testing had not been performed, the study site principal investigator was notified as soon as study outcomes were unmasked.

All participants enrolled in the SMART study consented to collect data related to the performance and utility of cfDNA testing for 22q11.2DS. This included confirmatory genetic testing, prenatal ultrasound examinations, and pregnancy outcome data, such as delivery information and complications in the newborn period prior to hospital discharge. Data on cfDNA and confirmatory genetic testing results, ultrasound data, and pregnancy outcome were collected for all SMART participants by trained research coordinators at each study site. Demographics, number of obstetrical ultrasounds, diagnostic prenatal testing results and pregnancy outcomes were compared for all SMART participants who received a cfDNA result that was either high-risk for 22q11.2DS or low-risk for all conditions screened, including trisomies 13, 18, 21, monosomy X and 22q11.2DS, and for whom both pregnancy outcome and genetic confirmation results were available.

To specifically address the frequency with which newborns underwent evaluations targeted to known 22q11.2DS-related phenotypic differences, an ancillary study was designed and received IRB approval in 2017 from all participating institutions. The supplemental data form is provided for review (Supplementary Figure S1) and included: fetal echocardiography, lymphocyte count, serum calcium level, postnatal echocardiography, palatal assessment, and diagnostic genetic testing for 22q11.2DS. The completion of the supplemental data form was requested for all pregnancies receiving a high-risk cfDNA result for 22q11.2DS that resulted in a live-born infant surviving the immediate neonatal period, that is, prior to hospital discharge. To determine the baseline frequency with which these neonatal evaluations were performed for each participant with a high-risk 22q11.2DS cfDNA result, coordinators collected these same supplemental outcomes for one study participant receiving a low-risk cfDNA 22q screening result, matched for maternal age, and date and site of delivery. No data were collected after discharge from the hospital. Incomplete data fields on the supplemental data form were excluded from both the numerator and denominator for those specific analyses.

2.1 | Statistical analysis

Continuous variables were compared using the Wilcoxon test and categorical variables using the chi-square test or Fisher's exact test, as appropriate. A nominal p value of <0.05 was considered to indicate statistical significance. SAS Studio 9.04 software (SAS Institute) was used for analysis.

3 | RESULTS

A total of 18,020 SMART study participants, enrolled between 2015 and 2019, met the criteria for analysis; 17,982 (99.79%) received low-risk and 38 (0.21%) high-risk cfDNA results for 22q11.2DS. In total, 12 cases were affected with 22q11.2DS, 3 had low-risk cfDNA screening results while 9 had high-risk results. Table 1 summarizes the demographics, prenatal evaluations and pregnancy outcomes for the SMART cohort, stratified by whether participants had received low- or high-risk cfDNA screening results for 22q11.2DS. Overall, 18.4% (7/38) of participants with high-risk cfDNA results had abnormalities identified on prenatal ultrasound as compared to 3.0% (522/17,982, $p < 0.001$) of those with a low-risk result. Those with

TABLE 1 Demographic and pregnancy clinical data for the low-risk and high-risk cfDNA result groups.

	LR22q $n = 17{,}982$	HR22q $N = 38$	p value[a]
Maternal age (years)	33.7 ± 5.4	33.3 ± 6.2	0.674
GA cfDNA screening (weeks)	13.3 ± 3.1	13.8 ± 4.5	0.847
Fetal fraction (%)	10.0 ± 4.1	9.0 ‡ 3.5	0.115
Prenatal diagnostic testing	352 (2.0%)	21 (55.3%)	<0.001
	Negative $n = 302$	Negative $n = 17$[b]	
	Abnormal $n = 50$ (not 22q11.2DS)	Confirmed 22q11.2DS $n = 3$	
# Ultrasounds per pregnancy			<0.001
1	3085 (17.2%)	3 (7.9%)	
2	13,901 (77.3%)	24 (63.2%)	
3 or more	996 (5.5%)	11 (29.0%)	
Prenatal ultrasound abnormality	522 (3.0%)	7 (18.4%)	<0.001
Pregnancy outcome	LB $n = 17{,}100$ (98.4%)	LB $n = 31$ (81.6%)	<0.001
	TAB $n = 32$ (0.2%)	TAB $n = 3$ (7.9%)	
	SAB $n = 4$ (0.02%)	SAB $n = 1$ (2.6%)	
	IUFD/NND $n = 30$ (0.2%)	IUFD/NND $n = 2$ (5.3%)	
	Unknown $n = 216$ (1.2%)	Unknown $n = 1$ (2.6%)	
Livebirths			
Cesarean delivery	6012 (33.6%)	10 (30.3%)	0.854
GA At delivery (weeks)	39.2 ± 1.8	39.2 ± 1.7	0.898

Abbreviations: GA, gestational age; HR, high-risk; IUFD, intrauterine fetal demise; LB, livebirth; LR, low-risk; NND, neonatal death; SAB, spontaneous abortion; TAB, therapeutic abortion.

[a]Fisher's Exact comparing LR and HR cfDNA screening result groups.

[b]22q11.2duplication confirmed by QF PCR $n = 1$.

high-risk 22q11.2DS results were more likely to undergo prenatal diagnostic testing (55.3%; 21/38 vs. 2.0%; 352/17,982, $p < 0.001$) and to have three or more prenatal ultrasound examinations (29.0%; 11/38 vs. 5.5%; 996/17,982, $p < 0.001$).

Summary data regarding selected outcomes for the 12 affected pregnancies are presented in Supplementary Table S1. The mean maternal age was 31.9 years (range 20–41). Four of the infants were male and 8 were female. The three cases who had high-risk cfDNA screening and prenatal confirmation by diagnostic testing chose to proceed with pregnancy termination; two of these had cardiac defects identified after cfDNA results. Of the 9 liveborn neonates with 22q11.2DS, three were low-risk by cfDNA, none of whom had pre- or postnatal clinical genetic testing. The remaining six were high-risk by cfDNA, three of whom did not have clinical pre- or postnatal diagnostic genetic testing before hospital discharge. The results of the research CMA were not available prior to discharge. All three surviving infants with postnatal diagnostic testing prior to hospital discharge had abnormal postnatal echocardiograms, and two had cardiac surgery; additionally, all were hypocalcemic, and two had calcium administered.

Supplemental data on neonatal management and outcomes were collected for 29/32 (90.6%) live born infants with high-risk 22q11.2DS cfDNA results, including three with confirmed 22q11.2DS (Supplementary Table S1; cases 2,4,9), as well as 35 low-risk control pregnancies (Figure 1). Of the 29 infants with high-risk 22q11.2DS cfDNA results, 16 had prenatal diagnostic testing and all were confirmed negative for 22q11.2DS. Table 2 summarizes select outcomes and results of newborn evaluations for 22q11.2DS-related complications, comparing the remaining 13 infants who were considered high-risk for 22q11.2DS at the time of birth and the 35 low-risk by cfDNA pregnancies. Of the 13 infants who were considered high-risk for 22q11.2DS at the time of birth, 46.2% (vs. 0% in the low-risk cfDNA cohort, $p < 0.001$) had postnatal genetic testing for 22q11.2DS, 30.8% (vs. 2.9%, $p = 0.02$) received postnatal echocardiography, 46.2% (vs. 5.7%, $p = 0.003$) had calcium levels measured and 53.8% (vs. 20%, $p = 0.03$) had a lymphocyte count measured. A single abnormal T-lymphocyte receptor (TREC) was recorded from an affected infant, with a lymphocyte count of 2.5.

4 | DISCUSSION

Our study demonstrates that a high-risk cfDNA screening result for 22q11.2DS results in changes in prenatal and neonatal clinical management. Pregnant women who received a 22q11.2DS high-risk

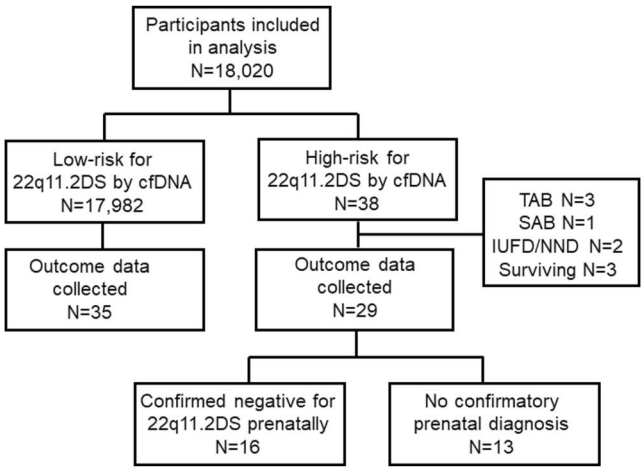

FIGURE 1 Flow diagram of patients in analysis. IUFD, intrauterine fetal demise; NND, neonatal death; SAB, spontaneous abortion; TAB, therapeutic abortion.

cfDNA result were significantly more likely to undergo pre- or postnatal confirmatory diagnostic testing and fetal and newborn assessments. However, our findings also suggest that these diagnostic evaluations were applied inconsistently. The proportion of high-risk infants who received a 22q11.2DS-specific clinical and laboratory assessment before discharge ranged from 30.8% to 53.9%. Of patients who received a high-risk 22q11.2DS cfDNA result, only 55% chose to pursue prenatal genetic testing and the 3 pregnancies confirmed to have 22q11.2DS resulted in pregnancy termination. After birth, only 46% of those who did not have prenatal genetic testing had postnatal diagnostic testing. Likewise, only 30.8% of them received postnatal echocardiography, 46.2% had calcium levels measured and 53.8% had a lymphocyte count measured.

Early confirmation of 22q11.2DS is vital not just influencing parents' decisions regarding pregnancy continuation but also substantially improving the prospects for those affected. Recent literature highlights targeted interventions that can significantly enhance outcomes,[10–17] guided by newly updated health surveillance protocols catering to different age groups.[20–28] The review by Blagowidow et al (26) comprehensively outlines risks, benefits and limitations of approaches to pre and postnatal management of high-risk infants. Counseling prior to prenatal genetic screening should emphasize that a high-risk screening result is not confirmatory, and that diagnostic genetic testing will be offered. The availability of targeted evaluations and interventions to improve outcomes for affected individuals should also be part of pre-test counseling. If a patient declines prenatal genetic testing after a high-risk screening result, prenatal sonographic surveillance and fetal echocardiography should be pursued.[28] Diagnostic testing, ideally using cord blood after delivery,[29] is important to optimize outcomes; an infant may have 22q11.2DS even if the physical examination is normal. However, we acknowledge that the timing of diagnostic genetic testing for an infant at high risk for 22q11.2DS may be tailored according to local differences in clinical practice. Before hospital discharge, while awaiting genetic testing results, evaluation for phenotypic (such as unrecognized submucous cleft palate and critical congenital heart disease) and laboratory abnormalities (including hypocalcemia) should be performed.

TABLE 2 Data for pregnancies with low-risk and high-risk and cfDNA results that were still considered low-risk and high-risk at birth.

	Infants low-risk by cfDNA $N = 35$	Infants high-risk by cfDNA without prenatal diagnostic testing.$N = 13$ includes 4 affected	*P* value
Supplemental Clinical Outcomes and 22q11.2DS-related Interventions			
Maternal age (years)	33.6 ± 5.9	29.8 ± 7.4	0.08
GA cfDNA screening (weeks)	12.7 ± 2.4	15.6 ± 6.5	0.26
Cesarean delivery	15 (42.9%)	9 (69.2%)	0.10
Newborn 5+ days in hospital	4 (11.4%)	4/12 (33.3%)	0.18
Prenatal echocardiography	5 (14.3%)	10 (76.9%)	<0.001
Postnatal echocardiography	1 (2.9%)	4 (30.8%)	0.02
Postnatal genetic testing for 22qDS	0	6 (46.2%)	<0.001
Calcium level obtained[a]	2 (5.7%)	6 (46.2%)	0.003
Calcium level below normal	0	3 (23.1%)	0.02
Lymphocyte count obtained[b]	7 (20.0%)	7 (53.8%)	0.03
Palate assessed	22 (62.9%)	10/12 (83.3%)	0.29
Feeding method			1.00[c]
Breast	27 (77.1%)	8 (61.5%)	
Bottle	8 (22.9%)	3 (23.1%)	
Tube	0	2 (15.4%)	

[a]Calcium levels ranged from 8.7 to 9.0 mg/dL among the 22qDS LR cohort, and from 7.1 to 9.8 mg/dL in the 22qDS HR cohort. Normal calcium levels <1 year of age: 8.7–11.0 mg/dL.[18]

[b]Lymphocyte counts ranged from 3.0 to 9.8 × 10^9/L among the 22qDS LR cohort, and from 2.2 to 16 × 10^9/L in the 22qDS HR cohort. Normal lymphocyte ranges 2.07–7.53 × 10^9/L for males and 1.75–8.00 × 10^9/L for females.[19]

[c]Comparison of breast versus other. Data are mean ± SD or *n*(%).

Recent pediatric management guidelines recommend a series of evaluations including pediatric echocardiogram and complete blood count (CBC) following a diagnosis, emphasizing that diagnostic delay could result in missed opportunities for intervention. Unfortunately, our data indicate that only 46.2% of high-risk infants have undergone the necessary diagnostic testing, showcasing a prominent gap in healthcare delivery. Despite the promising positive predictive value of 52% in identifying 22q11.2DS demonstrated by the SNP-based cfDNA using an updated algorithm,[6] many infants did not receive targeted

evaluations such as CBC and serum calcium-level assessments. Addressing this can reduce adverse outcomes, particularly the severity of developmental delay linked to untreated conditions such as hypocalcemia.[11–13] Furthermore, even though initiatives like the inclusion of TREC counts in newborn screening programs have fostered earlier identifications,[17] inconsistencies in newborn screening panels both within the United States and globally may pose significant challenges in achieving universal early diagnosis and management of these high-risk infants. Therefore, refining and universalizing screening protocols, including immunodeficiency, serum calcium measurements and other critical endocrine parameters post-diagnosis, should be a priority to prevent adverse outcomes and foster improved developmental trajectories.

Recently, the American College of Medical Genetics and Genomics suggested offering cfDNA-based prenatal screening for 22q11.2DS to all patients.[30] Similar to other recently published guidelines, this document does not include recommendations for comprehensive pre- or postnatal assessment when a high-risk cfDNA result is reported. We encourage the development of guidelines for the evaluation of newborns at high risk for 22q11.2DS due to high-risk cfDNA results when prenatal diagnostic genetic testing has declined. Prior to the availability of non-invasive screening using cfDNA, the average age of diagnosis of 22q11.2DS was approximately 4 years of age.[5,18] Prenatal screening, therefore, represents an opportunity to identify affected individuals early, allowing for immediate neonatal evaluations and the necessary interventions that can improve outcomes.

The clinical utility of prenatal genetic screening for 22q11.2DS cannot be fully realized unless high-risk cfDNA screening results that were not addressed prenatally are communicated to the pediatric team, allowing appropriate evaluation for, and management of, associated phenotypic differences.[19] While our study did not determine why 22q11.2DS-related evaluations were not performed for more than half of the high-risk newborns, it suggests that there is a need for improved communication between obstetric and neonatal care providers regarding the results of prenatal genetic screening tests and the implementation of protocols for evaluation of these infants.

There are limitations to this study that should be acknowledged. The study cohort was relatively small due to the frequency of the condition itself, 1 in 1524 pregnancies in the SMART cohort, and due to the low rate of high-risk cfDNA screening results (0.21%).[6] Although we found that women with high-risk cfDNA results underwent more prenatal ultrasound examinations, we do not know why these ultrasound examinations were ordered. We also do not know why postnatal evaluations and/or diagnostic genetic testing were not pursued. Specifically, we do not know if these evaluations were offered and declined, not offered, or if they were planned to be performed after hospital discharge. A concern would be a failure to offer testing by the pediatric provider either due to their not knowing the prenatal screening results or a false assumption that apparently normal infants without cardiac anomalies are at very low risk for 22q11.2DS. Finally, the study was not designed to assess long-term management and outcomes and it is possible that some of the 22q11.2DS relevant tests were pursued in an outpatient setting after discharge.

5 | CONCLUSIONS

This study reports comprehensive data regarding prenatal care in a cohort of women who chose cfDNA screening for 22q11.2DS, along with data regarding neonatal testing and management in liveborn infants from pregnancies receiving high-risk cfDNA results. The data indicate that while more prenatal and neonatal testing was pursued after a high-risk cfDNA screening for 22q11.2DS, approximately half of the high-risk infants did not undergo diagnostic genetic testing or evaluation for 22q11.2DS-related complications before hospital discharge. These data underscore the need for the development of guidelines for immediate postnatal care when a high-risk cfDNA screening result for 22q11.2DS is received, but prenatal diagnostic genetic testing is not conducted. These guidelines will contribute to improved communication between obstetric and pediatric healthcare providers regarding high-risk prenatal genetic screening results.

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CONFLICT OF INTEREST STATEMENT

All site principal investigators (Pe'er Dar, Bo Jacobson, Fergal Malone, Ronald J Wapner, Ashley S Roman, Asma Khalil, Revital Faro, Rajeevi Madankumar, Sina Haeri, Robert Silver, Nidhi Vohra, Jon Hyett, Cora MacPherson, and Mary E. Norton) received institutional research support from the funding sponsor (Natera). Melissa Egbert, and Zachary Demko are employed by the study's funding sponsor (Natera) and hold stock or options to hold stock. Kimberly Martin is a consultant to the funding sponsor (Natera) and holds stock and options to hold stock. Jon Hyett has an ongoing research collaboration that includes financial support for biochemical analytes from Perkin Elmer, has earned honoraria and/or given talks that were not compensated from Natera, Roche and Canon, and has participated in Asian/Australasian expert consultancies for Natera and Roche. Bo Jacobson collaborated in the IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagents for PLGF analyses. Ronald J Wapner received research funding from NICHD and support from Illumina for research reagents. Mary E. Norton is a consultant to Luna Genetics. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data of this study are available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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