

Opinion

## Screening Before We Know: Radical Uncertainties in Expanded Prenatal Genetics

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### Abstract

In this article, we discuss the radical uncertainties unleashed by expanded prenatal genetics. We show how we are now routinely screening fetuses in the absence of two essential sorts of information. At the population level, we do not have sound, unbiased data about the prevalence, penetrance, and clinical variability of most mutations. At the level of the proband, it is often too soon to discern relevant information about the fetus' phenotype. First, we outline the longstanding ethical objections to newborn screening for poorly understood genetic anomalies and disorders, and explain how it limits our understanding of their penetrance and variability. Next, we contrast the strong restrictions and regulations around newborn screening with the more laissez-faire framework for prenatal screening, using the rollout of non-invasive prenatal testing (NIPT) as the timeliest and most illuminating example. We show how new conditions are added to NIPT kits based on technological feasibility and profit motive, leading to widespread prenatal screening for incompletely understood genetic disorders. Finally, we explore the myriad dilemmas that 'screening before we know' creates for counsellors,



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caregivers, and prospective parents in the age of non-invasive prenatal genetic screening, and argue for an approach that openly embraces the radical uncertainties we face.

### **Keywords**

Commercialization; genetic counseling; NIPT; prenatal genetic testing; screening; selective termination; uncertainty

## **1. Introduction**

Any new genetic screening program must reckon with a gnarly catch-22. It goes something like this: you should not screen for a genetic mutation or variant if you do not know its penetrance, but you will never know its penetrance without major screening studies. Yet, when it comes to the new non-invasive prenatal genetics, we are now routinely screening for mutations before we know their true prevalence, penetrance, or range of expression. There is an individual rendering of this uncertainty as well—the beguiling flipside of the coin that real people must face in an age of biomedicalized reproduction. When a prospective mother undergoes non-invasive prenatal testing (NIPT)—a genomics technology used to screen for certain genetic conditions during pregnancy—and a positive result comes back, she usually has to make decisions before relevant clinical information is available about the fetus. At the level of the genotypes *and* the phenotypes, population *and* proband, we are screening before we know.

In this article, we take stock of this paradox. We begin by outlining the longstanding ethical objections to newborn screening research for poorly understood genetic anomalies and disorders, and explain how it limits our understanding of their penetrance and variability. Next, we contrast the strong restrictions and regulations around newborn screening with the *laissez-faire* framework for prenatal screening, using the rollout of NIPT as the timeliest and most illuminating example. Finally, we explore the dilemmas that ‘screening before we know’ creates for counsellors, caregivers, and prospective parents in the age of non-invasive prenatal genetic screening, and argue for an approach that openly embraces the radical uncertainties we face.

## **2. Screening Babies’ Genes**

Government-run newborn screening programs have long been guided by the public health principles laid out in Wilson and Junger’s famous 1968 report for the World Health Organization [1]. Wilson and Junger recommended that we only screen for conditions whose natural history is clearly understood, for which there is an acceptable treatment that changes patient outcomes when it is detected early or pre-symptomatically, and for which there is a reliable screening test whose cost is acceptable to the public. The great prototype for universal newborn screening was phenylketonuria or PKU. In 1963, Robert Guthrie reported a cheap and reliable PKU screening method that simply required a drop of a newborn’s blood squeezed onto a paper card [2], and the non-invasive implementation of a low-phenylalanine diet prior to the onset of symptoms was known to dramatically improve developmental outcomes. In short, PKU served as a kind of poster-child for low-cost, profound reward newborn screening programs.

Universal newborn screening is therefore limited to a handful of conditions in most countries, and even in the US with its expanded newborn screening program, the addition of new conditions is subject to an intensely detailed regulatory process<sup>1</sup>. Meanwhile, these mostly recessive Mendelian genetic disorders are very different from the conditions we find on NIPT kits.

But what about newborn screening *research* for the sorts of chromosome mutations<sup>2</sup> targeted by NIPT screening? To understand why screening studies for poorly understood genetic mutations and variants are not carried out, it is useful to return to the fascination with the 47,XYY chromosomal aneuploidy of the late-1960s and early-70s. It began when a series of papers by Patricia Jacobs, Michael Court Brown, William Price, and colleagues in mid-1960s Edinburgh reported a remarkably high rate of men with an 47,XYY karyotype in Scottish prisons and asylums [3-7]. Fast-forward a few years, and XYY had been dubbed the “criminal chromosome” in the popular press. It graced the front page of the *New York Times*, featured in several high-profile murder trials, and gained intense interest well beyond cytogenetics, most notably in the fields of psychiatry and criminology (see [8-10] for historical reviews and critiques).

And yet, concerns about ascertainment bias dogged the entire XYY research enterprise. The US National Institute of Mental Health commissioned two major screening studies, including a prospective newborn study at Harvard. There was an intense backlash, as groups concerned about children’s rights led by the ACLU and Science for the People assailed the studies for the potential harm to developing children, for diverting attention away from the social causes of crime, and for risking a return to the disgraced eugenics of a few decades earlier. Eventually, the studies were discontinued. XYY did continue to make appearances in popular fiction venues like *Aliens 3*, *Law and Order* and the like, but it retreated into relative obscurity as a research topic and as a medical condition.

Ever since, there has been a broad consensus that we should not screen young children for poorly understood genetic anomalies, especially in the absence of evidence of high penetrance or effective early intervention strategies.(See [11-13] for contemporaneous reviews) Even though figures like John Hamerton, then president of the American Society of Human Genetics, argued for the continuation of prospective screening studies into mutations like 47,XYY, we see how the social and ethical objections levied against such studies created enormous hurdles. The reasons were largely fleshed out during the XYY debacle; we do not want to risk creating self-fulfilling prophecies, lowering expectations for development, disrupting child-parent bonding, or unleashing costly processes of overtreatment and iatrogenic harm.

This is why neonatal screening for genetic conditions has remained limited mostly to clinically well-understood genetic and metabolic disorders like sickle cell disease, spinal muscular atrophy, phenylketonuria (PKU), and cystic fibrosis. Even in the US, which has expanded newborn screening to include several dozen disorders, screening is limited to

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<sup>1</sup> See: <https://www.hhs.gov/guidance/document/recommended-uniform-screening-panel> (accessed 9.9.21)

<sup>2</sup> We are using “mutation” in its broadest sense to include the chromosome anomalies like aneuploidies and structural variants that are included current NIPT platforms, as well as the single gene mutations that are now being targeted in NIPT research.

treatable conditions that we *think* are consistently serious<sup>3</sup>. This is not just a question about state or consumer screening. Even within research contexts, prospective newborn screening studies are subject to intense regulatory oversight and monitoring.

In sum, neonatal screening is highly regulated and restricted. But what about *prenatal* screening?

### 3. Screening Fetuses' Genes

For decades now, there has been intense public and scholarly controversy surrounding both prenatal genetic testing and selective termination [15, 16]. However, ethical and political debates have mostly sidestepped the question of how a fetus' DNA should be assessed, when in pregnancy, and especially *which* genetic anomalies should be included in prenatal testing programs and reported back to prospective parents. Likewise, there has been very little by way of regulation on those fronts. In practice, prenatal testing procedures—using microscopic cytogenetic techniques or microarrays, as examples—have tended to report back whichever chromosomal mutations they can reliably identify, as early as possible in pregnancy. The contrast with neonatal genetic testing could hardly be starker.

NIPT screening throws this contrast into even sharper relief. For decades, the need for invasive techniques that come with significant discomfort and a slight risk of miscarriage, i.e. amniocentesis or chorionic-villus sampling (CVS), meant that prenatal genetic testing was confined to a small minority of pregnancies—primarily women over 35 years old and pregnancies where family history or a non-genetic screen substantially increased the likelihood of a serious genetic disorder in the fetus. When non-invasive prenatal screening was first rolled out around a decade ago, it began to upend that calculus. By analyzing cell-free fetal DNA (cfDNA) that circulates in a pregnant woman's blood from 8-10 weeks' gestation, NIPT is used to predict the chance of a fetus having a genetic condition. Most women will receive a lower-chance result (i.e. screen-negative). Others, however, will receive a higher-chance/screen-positive result, indicating that a fetus is likely to have a genetic condition. In these latter cases, invasive diagnostic testing—amniocentesis or CVS—is offered to validate the NIPT result.

NIPT was initially introduced into clinical practice in Hong Kong in 2011, though non-invasive prenatal screening had been hotly anticipated ever since fetal DNA in the mother's blood was first reported in 1997 [17]. It quickly caught on much more broadly. With just a simple blood draw from the mother providing the necessary sample, uptake was dizzyingly swift. Today, it is used to screen hundreds of thousands of pregnancies around the world each year, with strong growth expected over the next decade. A recent report indicates that, in 2019, several hundred thousand pregnant women underwent NIPT screens in the US alone<sup>4</sup>. Outside of the US, there are estimations that the global market for NIPT will reach over \$5 billion by 2028 [19]. Many of

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<sup>3</sup> As Timmermans and Buchbinder [14] have shown, US newborn screening returns not only a massive volume of false positives, but also ambiguous true positives that create "patients in waiting" and force experts to revise disease profiles.

<sup>4</sup> If around 2500-3000 NIPT screens are conducted per million commercially insured members (PMC 2020:10 [18]), then even if we ignore out-of-pocket screens and the fact that many states' Medicaid programs also cover NIPT, we arrive at an estimate of around half a million NIPT screens in 2019.

the pertinent professional organizations like the American College of Medical Genetics and Genomics (ACMG), the American College of Obstetricians and Gynecologists (ACOG), and the National Society of Genetic Counselors (NSGC) now recommend offering NIPT screening to *all* pregnant women, regardless of age or other risk factors [20], creating potential liability issues for providers who refuse coverage. As a result, payers are increasingly likely to cover NIPT screens.

Crucially for our argument here, NIPT holds the potential to screen for a wide range of genetic conditions. When NIPT first hit the market back in 2011, it was limited to one well-understood condition: Down syndrome. This is reflected in a slew of research and opinion pieces on NIPT screening for Down syndrome [21-23] as well as a range of studies focusing with individuals living with Down syndrome (people with DS; siblings; parents), their perspectives on NIPT, and how their views sit with the ‘expressivist objection’ to prenatal screening [24-26]. Even today, Down syndrome remains the primary focus when debates about NIPT surface and intensify.

Yet, Down syndrome was just the tip of the iceberg—the highly visible, well-understood condition that stood as the lone genetic condition targeted by initial NIPT offerings. It was quickly followed by two other autosomal trisomies, the Edwards’ (trisomy 18) and Patau syndromes (trisomy 13), both of which are rarer than Down syndrome and consistently very severe, with most affected fetuses not surviving past early childhood. What came next, however, showed how radically NIPT screening could remake the prenatal landscape.

Ever since 2012, the range of conditions screened by NIPT has grown slowly-but-steadily, not just in number but also in scope. Verinata Health reported the results of a study that demonstrated their platform’s ability to detect sex chromosome aneuploidies (SCAs) like 47,XYY, 47,XXY (Klinefelter syndrome), 47,XXX (Triple X syndrome), and monosomy 46,X (Turner syndrome). By November 2012, these SCAs were added to their Verify® screening kit. The company’s rivals quickly followed suit, inaugurating an intense commercial competition and, therefore, a steady expansion of the chromosomal mutations covered by NIPT platforms. Unlike the chromosome 13 and 18 trisomies, the SCAs are certainly not the first genetic mutations that one might add to a prenatal testing kit based on any defensible measure of the associated conditions’ severity, or actionability. Quite the contrary; SCAs tend to be fairly mild, with many bearers reaching adulthood without any idea that they have a genetic disorder [27].

It is poignantly ironic that, some 40 years after the ethical and political backlash that banished it to the margins of human genetics, XYY was one of the first mutations included on the new wave of NIPT screening platforms. The reason is clearly *not* that it exemplifies standard screening criteria (far from it), but rather because it is relatively easy for NIPT platforms to identify<sup>5</sup>. Companies in the US appear to add new genetic mutations to their NIPT screening kits simply because they can. It is, above all, a question of whether their platform can detect an abnormality in fetus’ chromosomes or genes with an acceptable level of sensitivity and positive-predictive value (PPV).

The same goes for the other SCAs. In other words, the SCAs were added to NIPT platforms, it seems to us, because they are whole chromosome aneuploidies that can be picked up with

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<sup>5</sup> It was also likely a secondary result of NIPT companies seeking to meet a very different consumer demand: the early identification of fetal sex (raising another series of important ethical questions).

relative ease, not necessarily because of any systematic assessment of their suitability for prenatal screening. That has sweeping implications. For one, it helps explain why many government and private insurers do not cover expanded NIPT screens for the SCAs. For another, it shows how, by focusing overwhelmingly on the implications for Down syndrome screening, we are failing to fully grasp the myriad issues raised by NIPT.

Some of these chromosomal mutations are consistently very serious, while others could be deemed incompletely penetrant, but they are all characterized by variable expressivity. Many of these mutations are so variably expressive that they beg the question, “penetrance of *what phenotype?*” They even problematize the notion of penetrance itself [9]. Take a person with 22q11.2 deletion syndrome, for example—which, if any, of the some 200 associated features will they have? Is an extra Y chromosome or a 16p11.2 microdeletion penetrant in a given person if they are “normal” by the standards of modern psychiatry, but discernably less “sociable” or “adept” on an IQ test than their siblings? Indeed, an unknown number of people with these genetic conditions live their lives without the faintest idea that they have a “pathogenic” chromosomal mutation. The key point, which we will return to below, is this: in the absence of *postnatal* screening studies, there is no way to provide sound risk information about these sorts of complex genetic conditions. We simply do not know their true range of expression.

It is important to consider the key force driving prenatal genetic testing innovation and shaping the composition of NIPT testing panels: commercial competition and profit-seeking. While much of the foundational research underlying cfDNA screening was conducted in academic settings, it was quickly patented and spun off into the biotechnology sector [28]. So, while newborn screening programs and prospective screening studies are indelibly shaped by regulators and concerns for patient, stakeholder, and public cost-benefit balance, prenatal genetic screening is now largely driven by market competition and (presumed) consumer demand. Indeed, the competition between biotechnology concerns around NIPT screening has been particularly intense and, at times, acrimonious [29].

Today, industry-leading Illumina’s MaterniT Genome kit reports all autosomal aneuploidies, the four major sex chromosome aneuploidies, and seven microdeletions syndromes, including highly variable disorders like the 22q11.2 and 1p36 deletion syndromes. They now also report back *any* chromosomal deletions and duplications of 7Mb or greater<sup>6</sup>—a figure that will surely shrink as the cfDNA screening technology continues to develop. In sum, if companies can claim high sensitivity and reasonable PPV for a mutation, they will likely screen for it in their quest for market share<sup>7</sup>. The logical endpoint—non-invasive *whole genome sequencing*—has been pursued in major labs and discussed by leading figures in the field since at least 2012 [30, 31].

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<sup>6</sup> See <https://www.integratedgenetics.com/sites/default/files/2020-04/rep-1037-v4-0819.pdf> (accessed 6.25.21).

<sup>7</sup> Roche’s Harmony NIPT test is a very partial exception to this rule. Their offering “focuses on clinically relevant conditions” to reduce counseling time, as well as the number of false positives and follow-up invasive tests. There is a particular focus on maximizing PPV for the three major autosomal trisomies. Still, they offer screening for the SCAs and 22q11.2 microdeletions. See: <https://sequencing.roche.com/en/products-solutions/by-application/clinical/nipt/test-options-and-implementation.html> (accessed 6.24.21).

What is done with a positive screening result is left entirely to the discretion of individuals and their local health care providers. The weighty responsibility to terminate a pregnancy or prepare for the arrival of a child with a genetic disorder is placed upon the prospective parent/NIPT consumer, with commercial actors framed as mere service-providers (this, arguably, also reflects neoliberalist public health discourses in the US and Global North more broadly). Some countries, like the UK, limit their public health NIPT offerings to a more restricted set of conditions, including previously tested-for genetic conditions (e.g. Down syndrome, Edward's syndrome, Patau syndrome) and those known to be consistently severe. Many insurance companies in the US also limit coverage in a similar manner. However, the clear trend among commercial offerings (including in the UK's private sector) is to offer prospective parents—as consumers—screening results for more and more mutations as a marketable commodity (see Löwy [20] for a review of the different national regulatory and commercial landscapes for NIPT).

Commercialization has transformed the prenatal landscape. Put bluntly, offering screening for more conditions is framed as sound *value-for-money*<sup>8</sup>. But for whom? While offering 'more' may be heralded as a growing abundance of choice and autonomy for prospective parents<sup>9</sup>, the use of cfDNA screening for sex chromosome abnormalities, microdeletions and duplications, and we expect much more over the coming years, presents major pitfalls. For one, it places a significant added burden on our already scarce supply of genetic counselors—and possibly other healthcare providers too. For another, the burgeoning scope of NIPT platforms produces ever-greater uncertainty for prospective parents, counselors, and healthcare providers. We discuss the notion of uncertainty below, as well as its stark impact given the rapid rollout of NIPT screening.

#### 4. Embracing Radical Uncertainty

How can we make sense of a precautionary framework for neonatal screening alongside a *laissez-faire* approach for prenatal screening/testing? This is not just a point of contrast; it is precisely the absence of postnatal screening that makes it impossible to establish robust prevalence and penetrance estimates for many genetic conditions, and therefore to provide clear risk information to prospective parents. This dynamic means that, as NIPT expands further past a small handful of well-understood and highly penetrant autosomal trisomies, a series of clinical and ethical dilemmas will come to the fore. Here, we focus on the proliferation of highly charged, uncertain decisions that NIPT is going to unleash on prospective parents.

In a classic 1921 work, economist Frank Knight fleshed out the distinction between risk and uncertainty [33]. A decision made in the context of risk, he argued, is based on quantified

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<sup>8</sup> The Nuffield Council on Bioethics (2017) in the UK have openly questioned the reliability and compulsion to expand the use of NIPT to screen for more genetic conditions. See <https://www.nuffieldbioethics.org/wp-content/uploads/NIPT-ethical-issues-full-report.pdf> (accessed 7.12.2021).

<sup>9</sup> See, for example, Chen and Wasserman's (2017) paper in the *American Journal of Bioethics* for a thoughtful argument in favor of non-invasive whole genome sequencing, undergirded by an education and consent framework, in order to enhance prospective parents' autonomy [32].

knowledge. For prenatal genetic results, that might look something like: “this mutation is associated with a 20% risk of a serious heart malformation, a 40% risk of an autism spectrum disorder, and a 50% risk of mild-to-moderate intellectual disability.” Uncertainty, by contrast, is not amenable to this sort of firm quantification; we cannot firmly estimate the odds of the different outcomes—or even list all the possible outcomes—of a decision. When it comes to prenatal genetic findings, we need to lean into this distinction. What is often presented as risk-based information obfuscates a deep uncertainty. Why?

The reason is that much of the information we have about mutations’ phenotypic or clinical associations is riddled with ascertainment bias. For many of the mutations and conditions now covered by NIPT screens—and especially the more mild and variable ones—we simply do not have the sort of unbiased prospective data we would need to give people true risk information. Data is presented as risk-like information, but in so doing, a key distinction is glossed over, namely: “*n* percent of people with mutation *x* have phenotype *y*,” versus “*n* percent of people *who presented with the sort of phenotype that indicates mutation x, and who subsequently tested positive for it, have phenotype y.*” Suffice it to say that those are two very different claims. Indeed, a few limited studies have shown that prenatally ascertained SCA bearers—a far *less* biased sample—tend to be more mildly affected than their counterparts who were ascertained through the traditional, inevitably highly biased pathways [34]. We need to help prospective parents understand that we are giving them biased data about the effects of a given mutation—data that is presented in risk-like form, even as it glosses over deep uncertainties.

This brings us back to the two sides of the coin we mentioned at the beginning of this piece. In the context of a positive NIPT screen, we often lack both unbiased data about a mutation’s effects *and* information about the fetus’ phenotype. In cases where prenatal testing was ordered because of some other screening finding (e.g. via ultrasound), there is at least some Bayesian prior that a variable mutation is indeed pathogenic. However, most women undergoing NIPT screening moving forward will do so because it is cheap, easy, ‘reassuring’ [35], and recommended by the relevant expert organizations. If a positive result comes back and is then confirmed via a diagnostic test, they will be left to make a profound choice in the absence of clear information about either the mutation or their fetus. This is the new prenatal genetic uncertainty that many thousands of people will face over the coming years.

We do not want to weigh here in on the bioethics or healthcare systems debates about NIPT (for an introduction to some of these major debates, see: [7, 18, 36-39]). Instead, we simply argue that biotechnology companies and experts who counsel prospective parents should tackle the dual issues of ascertainment bias and clinical uncertainty in NIPT screening head-on. Anything less does not rise to the level of fully informed consent or honest counsel.

What does that mean in practice? First, we should be upfront with prospective parents: conditions are added to NIPT screening kits because the kits can detect them, not because of a systematic review of the mutations themselves or their compatibility with ‘a life worth living’. As Paul and Löwy [40] remind us, it is difficult to provide demonstrable and wholly accurate information to prospective parents on the quality of life with (and outcomes for) people living with a particular condition. As they astutely observe, there is a wide variance just in people living with Down syndrome—the most prominent and well understood genetic condition in debates around NIPT. Nonetheless, while there may be moments where true risk information

is available, the data produced by NIPT will rarely offer any guarantees, especially around prognosis. These issues become ever more acute as we move further and further beyond the autosomal aneuploidies, with all the many layers of uncertainty that entails. It is imperative that prospective parents know this, and that screening decisions are based on a range of considerations beyond the commercial logic of the prenatal testing industry.

Second, we need to develop ways to communicate the radical uncertainties arising out of ascertainment bias. While we have good reason to believe that some chromosomal mutations are consistently severe, and there are serious counseling guidelines for dealing with the complexity of conditions like Down syndrome, we need to be upfront with prospective parents about how much is *not* known about mutations like 47,XXX, 47,XYY, 22q11.2, or 1p36. As NIPT moves further into the realm of single-gene sequencing [41], we will need to communicate an even broader range of findings and data—multiplying prenatal uncertainty even before we get to the thorny question of “variants of uncertain significance” (VUSs). When it comes to prenatal genetics, uncertainty is not the same as confusion. On the contrary, it is the only honest rendering of our current knowledge about genetic difference. NIPT technology is designed to edge expectant parents who receive a negative screen that little bit closer to reproductive certainty, but it also produces profound uncertainties and dilemmas for the thousands who screen positive. Embracing that uncertainty head on will help prospective parents make informed decisions about selective termination—as will some understanding of *why* certain conditions are screened for (and who the actors were in making this choice). It will also help ensure that broad prospect horizons are held possible for the pregnancies that are continued.

In a sense, NIPT encapsulates one the central challenges of postgenomic medicine: our ability to give people information about genetic variants and mutations is growing by leaps and bounds, but our understanding of what that information means to human health and difference continues to lag far behind [7, 42]. Money and time must be invested not simply in genomic testing technologies, but also the training and support needed to accompany them [43]. That includes research, training, and support specifically targeted at the growing list of conditions included on NIPT screens. Improving the social fund of knowledge about genetic conditions alongside the rollout of prenatal screening, however, is easier said than done. Commercial interests have led us to juncture where a flood of prenatal data is being produced without the necessary tools to properly handle it. There is an acute shortage of genetic counsellors to help prospective parents understand and make reproductive choices. We lack the recommended early intervention resources and support services for people with genetic disorders, and there is still considerable legal ambiguity when it comes to genetic discrimination in insurance and employment. Finally, we need to safeguard protections for women who decide to terminate a pregnancy once a genetic condition is diagnosed. So much of modern reproduction was already characterized by an intense combination of science, risk, and uncertainty—and *screening*, rather than *testing*, only raises the stakes of uncertainty. As NIPT screening continues to expand both in volume and in the range of detectable genetic conditions, we therefore need to forthrightly acknowledge and confront the myriad uncertainties of the new prenatal landscape.

## Author Contributions

Daniel Navon drafted the manuscript, which was supplemented and revised by Gareth Thomas. The content of the manuscript is based on research conducted by both authors.

## Competing Interests

The authors have declared that no competing interests exist.

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