Implementation of a registry and open access genetic testing program for inherited retinal diseases within a non-profit foundation

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Abstract
The Foundation Fighting Blindness is a 50-year old 501c(3) non-profit organization dedicated to supporting the development of treatments and cures for people affected by the inherited retinal diseases (IRD), a group of clinical diagnoses that include orphan diseases such as retinitis pigmentosa, Usher syndrome, and Stargardt disease, among others. Over $760 M has been raised and invested in preclinical and clinical research and resources. Key resources include a multi-national clinical consortium, an international patient registry with over 15,700 members that is expanding rapidly, and an open access genetic testing program that provides no cost comprehensive genetic testing to people clinically diagnosed with an IRD living in the United States. These programs are described with particular focus on the challenges and outcomes of establishing the registry and genetic testing program.

KEYWORDS
clinical consortium, inherited retinal diseases, open access genetic testing, patient registry, venture philanthropy

1 INHERITED RETINAL DISEASES

The inherited retinal diseases (IRD) are a group of rare genetic diseases that affect the neural retina of the eye limited to members of the Registry who lived in the United States and often lead to a progressive loss of vision that may result in blindness. Within the United States it is estimated there are 200,000–300,000 people affected by an IRD, which projects a worldwide prevalence estimate of 4.5–6.8 million people (Daiger, Bowne, & Sullivan, 2007; Daiger, Sullivan, & Bowne, 2013). A recent analysis of just the autosomal recessive (AR) IRD reported a genetic prevalence of 1 case in 1,380 individuals, with 5.5 million people predicted worldwide (Hanany, Rivolta, & Sharon, 2020) with 2.7 billion people worldwide (36% of the population) healthy carriers of at least one mutation that can cause AR-IRD, possibly among the highest across any group of human Mendelian diseases. Each of the IRD are orphan diseases. The majority of the diseases are monogenic and over 270 genes have so far been implicated (RetNet, https://sph.uth.edu/RetNet/) (Daiger, Rossiter, Greenberg, Christoffels, & Hide, 1998), accounting for 55–60% of the disease burden (Bujakowska et al., 2016; Haer-Wigman et al., 2017; Zampaglione et al., 2020). Clinically the diseases can be diagnosed in three broad categories, those that affect the central retina initially and increase peripherally over time; those that affect the periphery first, then spread centrally, and those that are congenital and stationary. Within each of those categories there is great diversity in age of onset, rate of progression, and mode of inheritance (Sahel, Marazova, & Audo, 2015). Traditional clinical diagnosis has been based on named disease nomenclature representing the initial clinical presentation, such as Leber congenital amaurosis, for early childhood onset disease, retinitis pigmentosa (RP) for diseases
starting peripherally and moving centrally and Usher syndrome, for
diseases that involved hearing loss in addition to vision loss. With
the increased knowledge about the genetic cause of disease, however,
there has been a greater focus on a gene-specific disease nomenclature.
For instance, pathogenic variants in the gene USH2A, while
initially identified as the cause of Usher syndrome type 2A, are
now known to be the most common cause of disease in AR non-syndromic
RP (Pontikos et al., 2020). Similarly, the genes CRX and PRPH2 are
each implicated in at least three different retinal diseases—Leber congenital
amaurosis, RP, and cone/cone-rod dystrophies (Leroy, Pennesi, & Ohnsman, 2018).
For most of the diseases, there is no clear

Prior to the 2018 approval of the gene augmentation therapy
Luxturna® (voretigene neparvovec) by the FDA for retinal disease
cased by biallelic pathogenic variants in the RPE65 gene there were
no approved therapies for any IRD. While still the only FDA approved
therapy, there is now a vigorous pipeline of clinical trials with promis-
ting therapies, due in large part to a 50-year history of investment and
advocacy by people affected by IRD in the Foundation Fighting
Blindness.

2 | THE FOUNDATION FIGHTING
BLINDNESS

Earnest research into ocular diseases started in 1968 with the establish-
ment of the National Eye Institute (NEI). In 1971, to increase
awareness and research into the rare IRD RP, a group of affected
families, led by the Berman and Gund families, formed the National
Retinitis Pigmentosa Foundation. In 1974, the Foundation established
one of the first dedicated research laboratories in the United States,
the Berman-Gund Laboratory led by Dr Eliot Berson at Massachusetts
Eye and Ear at Harvard Medical School, which in 1990 described the
first genetic basis of RP (Dryja et al., 1990) and initiated the near
exponential increase in IRD gene discovery. As the increasing genetic
diversity and overlap between RP and other IRD grew, the Foundation
was renamed to the Foundation Fighting Blindness. The Foundation
continues to invest ~25% of its funds in gene discovery and charac-
terization, supporting increasingly sophisticated genetic tools to
discover the genetic cause of the remaining 40-45% of unsolved IRD
cases (Bronstein et al., 2020), and supports a nationwide Israeli IRD
consortium performing clinical and genetic mapping of the entire
Israeli IRD population (Sharon et al., 2020). In total the Foundation
has raised over $760 M for IRD research with an annual research
budget of over $20 M that supports over 73 investigators across
14 countries.

The current mission of the Foundation is to support the develop-
ment of treatments and cures for the inherited retinal dystrophies and
age-related macular degeneration where there are clear genetic
drivers of disease. To achieve this goal, the programs of the Founda-
tion cover a broad spectrum (Shaberman & Durham, 2019) and
include: clinical career development awards for young and established
investigators; individual and multiple investigator preclinical and clinici-
cal research awards; mentored translational research acceleration
awards pairing experienced industry drug developers with promising
academic research (https://www.fightingblindness.org/grants-and-
award-programs); non-rodent animal model awards to support the
development of new genetic models with larger eyes; and a
canine IRD facility (Beltran, 2009) co-funded with the NEI to acceler-
ate bench to bedside research in a large clinically relevant eye
(https://www.vet.upenn.edu/research/centers-laboratories/research-
laboratory/experimental-retinal-therapies/publications#2001). Funding
decisions and strategic directions for preclinical and clinical research
are guided by a scientific advisory board of 54 international leading
researchers and clinicians in IRD (https://www.fightingblindness.org/
about/scientific-advisory-board).

3 | CLINICAL CONSORTIUM

Accurate diagnosis, characterization and treatment of patients with
IRD requires both clinical and genetic characterization of disease. In
2013 the Foundation funded an international nine center natural
history study of Stargardt disease due to pathogenic variants in the
ABCA4 gene, ProgStar (NCT01977846) (Strauss et al., 2019) that
resulted in over 14 publications and the identification of relevant
clinical endpoints (http://progstar.org). Building on this model, in
2016 the Foundation created a clinical consortium which currently
consists of over 38 IRD centers of excellence across 11 different
countries (https://public.jaeb.org/ffb/clin). The goal of the consortium
is to accelerate clinical translation of promising therapies by undertak-
ing robust, high-quality, multi-center clinical studies that are shared
openly. Studies generate data using standardized protocols, a central
coordinating center (JAEB) and study-certified reading centers. De-
identified data from the completed trials are archived in an open central
repository to stimulate further hypothesis generation and innovation.
Currently a natural history study of diseases caused by pathogenic
variants in the USH2A gene, called RUSH2A (NCT03146078) is following
127 patients over 4 years is in progress (Duncan et al., 2020) and a sec-
ond study on people with pathogenic variants in the EYS gene called
Rate of Progression in EYS Related Retinal Degeneration (Pro-EYS)
(NCT04127006), a cause of AR RP, is also in progress.

4 | THE RD FUND

Historically the Foundation has raised funds through traditional
community-based nonprofit approaches which it invested in awards
to investigators that range from $30,000 to $500,000 per year. How-
ever, to accelerate the pace of clinical progress in moving from labora-
tory drug development to approved clinical products, costs are tens, if
not hundreds, of millions of dollars for each program, and have a very
high failure rate. To meet this challenge requires innovation in funding
models, such as leveraging investments to attract outside venture
capital. To accomplish this, the Foundation launched the Retinal
Degeneration Fund (RD Fund) in 2018 (https://www.retinaldegenerationfund.org/) as a 501(c)(3) not-for-profit venture philanthropy organization. With over $70 million of capital to invest, the Fund focuses on making mission-related investments, preferably for programs within 18 months of initiating clinical proof of concept studies, with any returns reinvested in the Foundation. Currently the portfolio contains eight companies with investments ranging from $250 K up to $7.5 M.

5 | MY RETINA TRACKER REGISTRY

One challenge for rare genetic diseases is identifying the affected population. Few eyecare professionals see a case of an IRD or can provide a clear diagnosis. A study by Achroma Corp commissioned by the company AGTC in 2018 showed that for adults with achromatopsia, the patient journey took over 5 years and on average seven different healthcare providers for a diagnosis. Notably only 58% of adults and 65% of children with achromatopsia received genetic testing to support the clinical diagnosis (Achroma Corp, 2018).

Many people affected with an IRD do not complete the diagnostic journey but instead seek practical support at low vision centers. This creates barriers to accelerating treatments and cures. It also impacts our understanding of the true prevalence, clinical diversity, geographic distribution, age and rate of progression of disease in the population, and the ease of enrolling eligible patients into research and clinical studies. Upon commercialization of a therapy this lack of information about these conditions slows the speed of market penetration, which are key considerations for investors financing drug development. A registry easily accessible to people affected by the IRD can help address these issues.

The Foundation had maintained a patient registry for many years, that grew to 11,000 names, but was little more than a contact list of patients with IRD, but had limited disease information. In 2014, to improve data quality and depth a more detailed on-line registry was launched, under an Institutional Review Board (IRB) approved protocol, branded My Retina Tracker® Registry https://www.fightingblindness.org/my-retina-tracker-registry (Fisher, Bromley, & Mansfield, 2016). The goals of the Registry are to provide a single, integrated source of information about, and connection to, all people with an IRD; and to share those data, de-identified, with researchers and partners, in order to accelerate the development of treatments and cures. The Registry provides a convenient, secure database to aggregate information about people affected with an IRD (Figure 1).

Membership is initiated when an affected person chooses to join and provides online informed consent to share de-identified data, and be contacted by Registry staff if there is an opportunity, they may be interested in. Members own and control their own data. Once consented, members complete a series of short surveys to capture their subjective experience of living with their retinal disease, information about their health history, how they adjust their life around their disease, family history, and genetic cause of disease. During a clinical consult, members can ask their clinician to enter the objective clinical measurements through a clinical portal (Figure 1). A research portal enables data analysis of all Registry de-identified data for approved, external researchers. Members are encouraged to update their personal surveys at least once a year and the longitudinal data provides a perspective on disease progression. The member and clinician surveys use a controlled vocabulary primarily in the form of standardized drop-downs for answers, to facilitate efficient data mining.

In 2020, the Registry underwent a major upgrade. Key upgrades included enhanced security features; global compliance with data...
privacy rules, including GDPR and U.S. data and patient protection laws; and mobile-SMS integration to facilitate new and existing surveys and provide a more interactive platform. The validated Patient-Reported Outcomes Measurement Information System® 29 question survey (PROMIS-29), a tool designed to measure self-reported physical, mental and social health and wellbeing (Cella et al., 2019) and determine quality adjusted life years (QALYs) (Craig et al., 2014) was implemented. Other validated patient reported outcomes (PRO) and outcomes research instruments are planned.

Since launch, over 15,700 people have created an online Registry profile. The baseline growth of the Registry is ~100 new members per month, but with the introduction of no-cost genetic testing, that growth has averaged over 370 per month and continues to increase. The Registry also houses the contact information for the 11,000 registrants from the earlier registry, although many of those have failed to re-engage, possibly representing the age and history of the information.

The total 26,700 Registry membership is 48% male, 45% female with the remainder choosing not to declare their sex and the average age 50.2 years (±20.6 SD). For the 15,700 actively engaged members who have created a profile since the Registry went online, the membership is 44% male, 43% female with the remainder choosing not to declare their sex and an average age of 44.3 years (±20.7 SD). These differences in the two membership groups align with the history of the Registry. While most enrollees reside in the United States (94%), 112 countries are represented, with 18 countries representing 75% of the international membership. The most represented in international membership are: Canada (14%), United Kingdom (8.9%), India (8.2%), Italy (7.1%), Mexico (6.5%), South Africa (5%), Australia (4.5%), Poland (4.2%), Germany (3.5%), Argentina (2.2%), Brazil (1.8%), France (1.7%), Netherlands (1.6%) and New Zealand (1.3%). Of the international members, 97% have joined recently with an online profile, the members from the earlier registry being predominantly from Canada.

The composition of the current Registry data by clinical diagnosis is shown in Figure 2. RP, including Leber congenital amaurosis, accounts for 51% of the members’ diagnoses. Stargardt disease and all forms of Usher syndrome account for 10% each followed by juvenile inherited macular dystrophy at 6%. Currently 5% of cases are clinically characterized as unknown.

Data in the Registry is currently accessible via the Registry staff. Non-profit use is supported at no cost, while for-profit users sign a consulting contract to help offset the costs of Registry operation. De-identified data, lacking names, contact information or demographics below state/province level can be requested. If researchers are interested in contacting Registry participants, an IRB approved contact letter must be submitted to Registry staff outlining the identity of the interested party, their reason for contacting the Registry member, and contact information for the member to use if they wish to pursue the opportunity. Once approved, Registry staff send a...
contact themselves or not rests entirely with the member, and subsequent interactions with the interested party are independent of the Registry.

External interest in the Registry grew rapidly. There have been over 44 substantial requests for data including requests to: help enroll in nine clinical trials, multiple natural history studies and multiple focus groups; provide prevalence for specific genes, variants and technology-specific attributes; provide DNA for preclinical research; promote IRD disease specific conferences; and support a Retina International survey on the economic impact of blindness.

6 | REMOVING THE ACCESS BARRIER FOR GENETIC TESTING

The current preclinical and clinical pipelines for the IRD are heavily weighted toward gene and variant specific diseases. The first FDA approved in vivo gene augmentation therapy is specific to the RPE65 gene, and there is a pipeline of 15 different gene augmentation trials for the IRD in over 24 different clinical trials. Similarly, the first human in vivo CRISPR/Cas9 gene editing clinical trial, sponsored by Editas Medicine and Allergan is for a specific variant in intron 26 (c.2991+1655AG, p.Cys998X) of the CEP290 gene, as are antisense oligonucleotide-based variant specific trials by ProQR for the USH2A gene exon 13 mutation (c.2299delG, p.Glu767Serfs*21), RHO gene (c.68C>A, p.Pro23His), and CEP290 gene (c.2991+1655AG, p.Cys998X) variants. The genetic cause has become a critical component augmenting a clinical diagnosis. Prior to 2017 ~10% of My Retina Tracker Registry members reported having a genetic test.

In January 2017 the Foundation launched a pilot program to understand the patient and clinical interest in genetic testing by funding a comprehensive IRD genetic testing and counseling service at no cost to patient, clinician or insurance. The program was limited to people living in the United States and designed to address the problems faced within the United States for access to testing. Models seeking to minimize the cost using patient insurance were considered, but reimbursement rules, and the Foundation acting essentially as a co-insurer, created administrative complications and would specifically exclude Medicaid patients who only receive last resort coverage.

To reduce the Foundation’s administrative workload, and provide a consistent dataset for later analysis, a single genetic testing provider was selected. Key considerations were for a comprehensive IRD gene panel test with strong coverage of the genetic regions known to be difficult, such as the 1kb long purine rich region of ORF15 within the RPGR gene (Vervoort et al., 2000; Vervoort & Wright, 2002) which is reported to account for 80% of all cases of RPGR mutations, sensitivity for the increasing number of deep intronic pathogenic variants being discovered in genes like ABCA4 (Sangermano et al., 2019), and high sensitivity copy number detection, since these variants may represent 9% of IRD cases (Zampaglione et al., 2020).

Turn-around time was also important. In the past, Registry members had sought Registry staff help to obtain results for genetic testing they had participated in many years prior. Expecting results in weeks, members expressed frustration and lack of confidence in testing when there had been no communication of results after a year, often more, and their enquires not returned. In most cases the member had participated in an academic research study, which had failed to identify a genetic cause. Communicating the difference between research studies and a CLIA-certified test, and education that a CLIA-certified test would provide a prompt result, even if negative, was important. Given the complexity of a genetic result, and the enquires we had previously from constituents who had been tested, but results had not been explained to them, genetic counseling was considered an essential aspect for our program. Genetic counseling was provided through genetic counselors associated with IRD centers when available, or otherwise provided by InformedDNA telegenetic counselors who could support patients nationwide. Blueprint Genetics was selected as the genetic testing lab.

The pilot program was an IRB approved protocol within the Registry Protocol. Eligibility was limited to members of the Registry who lived in the United States, who completed an informed consent, had not previously had a relevant comprehensive gene panel test, and agreed to upload the result into their de-identified Registry profile. To order the test a clinician was required to enter, at minimum, a clinical diagnosis of an IRD and a recent best corrected visual acuity (BCVA) into the Registry clinical portal. Registry staff confirmed all eligibility criteria before approving Blueprint Genetics to test and invoice the Foundation. During genetic counseling, the test result was entered into the Registry clinical portal, before invoicing the Foundation. Initially 10 clinicians with a strong IRD expertise were approved to order the test. Demand from patients and clinicians to expand the program led, over 22 months, to over 180 approved clinicians across 149 geographically diverse practice groups, of which 40% were academic and 60% private, ordering over 6,300 tests. An analysis by InformedDNA of referral data from two of the clinics with the highest referral rates, showed that prior to the program 75% of patients referred for testing reported they did not complete pre-test genetic counseling appointments or obtain genetic testing, primarily because of lack of insurance coverage and/or cost, with genetic counseling, or testing, or both. The program reversed the trend with >98% participation of referred patients completing genetic testing through this research protocol. In 2019 a survey of the satisfaction with genetic counseling showed that 98% considered the counseling important, feeling more informed about their genetic risks and better equipped to make informed decisions about their retinal condition.

As demand from the program grew, the Foundations administrative burden ensuring eligibility and tracking invoicing became un scalable. Common challenges were patients not being in the Registry, clinicians overlooking the entry of the diagnosis and/or BCVA in the Registry and the need for ordering clinicians, especially in academic centers, to seek their IRB approval before submitting patient data into the third-party Registry. These created significant backlogs in the testing pipeline, delaying results to patients.

To scale more efficiently an Open Access genetic testing program was launched in October 2019 using a recently expanded retinal dystrophy panel (including mitochondrial genes) of 322 genes offered by
Industry is currently focused on a handful of the 270 IRD genes, with multiple industry partners overlapping therapeutic gene targets, but careful design can ensure all parties benefit, while also benefitting the entire IRD patient population with a genetic understanding of their disease and shared with the entire research community through My Retina Tracker Registry. The Foundation, in collaboration with Blueprint Genetics and InformedDNA is currently forging a new model to achieve this partnership model. Several early industry partners supporting the development of this program are acknowledged on the Open Access Genetic Testing Program website (https://www.fightingblindness.org/open-access-genetic-testing-program). One limitation of this program is its restriction to the United States and the need to address the unique challenges presented by the structures of the U.S. healthcare and insurance environment. In the future the Foundation is interested in exploring extension of this program to a broader international community, which may require different considerations and a different structure to address those environments.

7 | GENETIC TESTING OUTCOMES

Currently over 8,600 of the approximately 15,700 Registry members have had a genetic test, with over 7,600 of those being provided by

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Genetic causes of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of genes</td>
<td>% Solved genetic cases</td>
</tr>
<tr>
<td>Top 5 genes</td>
<td>48.2</td>
</tr>
<tr>
<td>Top 10 genes</td>
<td>59.9</td>
</tr>
<tr>
<td>Top 20 genes</td>
<td>72.1</td>
</tr>
<tr>
<td>Top 25 genes</td>
<td>76.0</td>
</tr>
<tr>
<td>Top 54 genes</td>
<td>88.9</td>
</tr>
</tbody>
</table>

Note: The causative genes for the first 5,879 cases submitted to the My Retina Tracker Genetic Testing Program are provided in rank order for the cases that received a clear genetic result (pathogenic or likely pathogenic variants). The incidence of each gene (%) is provided for the top 25 genes with key steps in incidence indicated for the bottom 29 genes.
TABLE 2  Diagnostic yield of genetic testing by clinical diagnosis

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Number diagnosed</th>
<th>Genetically confirmed</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usher syndrome</td>
<td>320</td>
<td>264</td>
<td>82.5</td>
</tr>
<tr>
<td>Other syndromic retinal dystrophy</td>
<td>97</td>
<td>81</td>
<td>83.5</td>
</tr>
<tr>
<td>Vitreoretinopathy</td>
<td>103</td>
<td>78</td>
<td>75.7</td>
</tr>
<tr>
<td>Choroidal dystrophy</td>
<td>93</td>
<td>55</td>
<td>59.1</td>
</tr>
<tr>
<td>Rod/rod-cone dystrophy</td>
<td>3,048</td>
<td>1,787</td>
<td>58.6</td>
</tr>
<tr>
<td>Macular dystrophy</td>
<td>1,452</td>
<td>837</td>
<td>57.6</td>
</tr>
<tr>
<td>Cone/cone-rod dystrophy</td>
<td>670</td>
<td>333</td>
<td>49.7</td>
</tr>
<tr>
<td>Overall</td>
<td>5,783</td>
<td>3,435</td>
<td>59.4</td>
</tr>
<tr>
<td>Other, not grouped, or unknown</td>
<td>96</td>
<td>38</td>
<td>39.6</td>
</tr>
<tr>
<td>Total</td>
<td>5,879</td>
<td>3,473</td>
<td>59.1</td>
</tr>
</tbody>
</table>

Note: The detection rate, by clinical diagnosis, for the first 5,879 cases submitted to the My Retina Tracker genetic testing programs. Other syndromic retinal dystrophies are represented by Bardet Biedl Syndrome (42 patients), Gyrate Atrophy (8 patients), Joubert syndrome (2) and various other single case or unclassified syndromes. Vitreoretinopathies were represented by Retinoschisis (91 patients), Stickler (4), FEVR (3), Unspecified Vitreoretinopathy (3), Norrie Disease (1) and Wagner Disease (1).

the Registry genetic testing programs. A breakdown of the genetic causes of disease for the first 5,879 probands tested is shown in Figure 2. One hundred and forty-eight genes were implicated in a clear genetic diagnosis. Of these the top five genes: ABCA4 (20%), USH2A (13%), RPGR (7%), PRPH2 (5%) and RHO (5%) accounted for almost 50% of the genetic diagnoses, and the top 25 genes accounted for just over 75% of the genetic causes (Table 1). These results for the U.S. population are similar to the findings of a similarly sized U.K. IRD population study (Pontikos et al., 2020). Notable differences within the top five genes were a 1.5-fold higher incidence of RHO in the U.S. population, consistent with the founder effect of the RHO P23H variant (Farrar et al., 1990), accompanied by a similar 2.2-fold increased incidence of EYS, the most common cause of AR RP. While the incidences may be more broadly representative of the genetic incidence of IRD in the United States than single site studies (Stone et al., 2017), we anticipate more accuracy as the Open Access genetic testing program expands to a wider spectrum of referring clinicians.

The overall diagnostic yield, using testing laboratory variant classifications, was 59.4% across all IRD. This was calculated for autosomal dominant disease and X-linked disease by requiring one pathogenic or likely pathogenic variant, while for AR disease it was based on two pathogenic and/or likely pathogenic variants or the combination of a pathogenic or likely pathogenic with a variant of unknown significance. By clinical diagnosis, syndromic diseases such as Usher Syndrome and Bardet Biedl Syndrome had the highest detection rates of ~83%, while cone and cone/rod dystrophies had the lowest detection rates ~50% (Table 2). A more detailed analysis of the results is being prepared for publication.

8  |  CONCLUSION

Non-profit organizations, like the Foundation Fighting Blindness, can play critical roles in helping to catalyze and de-risk drug development in rare disease spaces like the IRD by a variety of strategies that include incentivizing clinician scientists to commit to these fields, supporting early preclinical and clinical work, sponsoring natural history studies that share data widely, and leveraged investments supporting key proof of concept studies in humans. Clinical characterization of patients, supported by a comprehensive genetic testing program, and natural history studies are also critical. Through implementation of a patient Registry, the patient perspective of disease, and ease of accessibility to rare disease patients can be facilitated. Foundations can partner with other organizations and industry partners and, by removing cost barriers, ensure all people diagnosed with an inherited disease can receive an accurate genetic diagnosis.

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