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FEATURE ARTICLE

Knowledge-technology-based discovery of unauthorized genetically modified organisms

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Introduction

Various legislations worldwide provide a framework for the authorization of genetically modified organisms (GMOs) and products derived therefrom [1]. Despite these regulations, novel GMOs occasionally enter the market without authorization [2–22] (Table 1) and are referred to as unauthorized GMOs (UGMs). The presence of UGMs in food and feed raises safety and labeling concerns, and challenges international trade [23, 24]. Recently reported UGM incidents have created an urgent need to harmonize regulations at a global level, and call for appropriate strategies to discover UGMs. However, some novel UGMs are intrinsically difficult to detect using current analytical strategies for reasons outlined herein. We therefore propose a paradigm shift in the way UGMs can be discovered: a documentation-based screening for products that potentially contain UGMs using knowledge technologies, followed by analytical confirmation. Here, we will describe the main concepts of the novel approach, illustrate it with a case study, and outline benefits, limitations, and complementarities compared with the current analytical detection strategy.

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Table 1 History of unauthorized genetically modified organism (*UGM*) incidents in the food and feed chain

UGM	Incident
Starlink corn[a] (October 2000)	A GM corn line (Starlink, Aventis CropScience) authorized for use in animal feed in the USA was found in food products on the initiative of a coalition of seven American antibiotechnology groups [3]
Experimental GM corn (vaccine)[b] (December 2002)	After compliance inspection, the USDA Animal and Plant Health Inspection Service found that soybean lots were contaminated with small amount of GM corn producing an experimental vaccine against the common transmissible gastrointestinal virus in pigs [2, 10]
GM papaya[a] (February 2004)	Marketing of GM papaya imported from the USA was detected in Germany, although no authorization for GM papaya had been granted in the EU. After the first notification in 2004 to the Rapid Alert System for Food and Feed, several other notifications were made until June 2009 [15, 18]
Bt-10 corn[b] (March 2005)	The Swiss group Syngenta sold seeds of an unapproved GM corn line Bt-10 as Bt-11, an approved GM corn line, to US farmers following mislabeling of its products. Several shipments of US Bt-11 corn were found to contain the Bt-10 unapproved line in Japan and Europe [5, 13]
GM sweet potato[b] (December 2005)	In December 2005, nonauthorized GM sweet potato was detected in Poland. The GM line was imported from the USA via the Netherlands
Bt rice (GM Shanyou 63)[b] (August 2006)	German authorities declared having found an unapproved Bt rice line (GM Shanyou 63) in rice products imported from China, 1 year after Greenpeace had claimed that this GM line had been found in products sold in food stores in China [7, 12, 14]. Since the first alert, repeated notifications were made to the Rapid Alert System for Food and Feed until June 2009
LLRICE601 rice[b] (September 2006)	The presence of the unapproved GM rice line LLRICE601 (Bayer Cropscience) was revealed during routine analysis. Traces were found in US rice exports in several countries, including European counties [6, 11, 16]. Notifications were repeatedly made to the Rapid Alert System for Food and Feed until December 2008
59132 (Event 32) corn[b] (February 2007)	Dow AgroSciences has voluntarily withdrawn certain hybrid corn seed lots potentially containing adventitious low levels of a US-regulated biotechnology event, 59132 (Event 32) [4, 9]
LL62 rice[a] (May 2007)	The presence of the EU-unauthorized GM rice line LL62 (Aventis Cropscience), in provenance from the USA (where it is deregulated), was revealed during routine market and border controls in Europe. Several notifications were made to the Rapid Alert System for Food and Feed during 2007
DAS 59122 corn[a] (May 2007)	The presence of the EU-unauthorized DAS 59122 corn line (Dow AgroSciences), in provenance from the USA (where it is deregulated), was revealed during routine market and border controls in Europe. Several notifications were made to the Rapid Alert System for Food and Feed during 2007
A2704 soybean[a] (August 2007)	The presence of the EU-unauthorized A2704 soybean line (Bayer CropScience), authorized in several jurisdictions outside the EU, was revealed during checks of the Austrian market a few months before its European authorization for import and processing in food and feed was granted
GM *Arabidopsis thaliana*[a] (March 2008)	Unauthorized GM *Arabidopsis thaliana* (P-35 S, T-NOS) food supplement containing recombinant human intrinsic factor from Denmark was found on the Polish market [17]
MIR604 corn[a] (October 2008)	The EU-unauthorized MIR604 corn line (Syngenta Seeds), authorized in several jurisdictions outside the EU, was detected several times during official checks of the market and border controls in the EU from October 2008
Mon88017 corn[a] (May 2009)	The EU-unauthorized Mon88017 corn line (Monsanto), which is authorized in several jurisdictions outside the EU, was detected during border controls in the EU in May and June 2009
FP 967 flax[b] (September 2009)	The EU unauthorized FP 967 flax line (University of Saskatchewan, Canada), which is authorized in USA and Canada, is being continuously detected in cereals and bakery products in the EU since September 2009. No GM flax has been registered in Canada since 2001. Several notifications were reported to the RASFF.

GM genetically modified

[a] Asynchronously authorized: authorization for commercialization reported in another jurisdiction

[b] Nonauthorized event: no authorization for commercialization reported

The current strategy for UGM detection

The GMO "life cycle" typically has four phases: the research and development phase, the authorization phase, the commercialization phase, and "phase out," or termination of commercialization by the company. Regulatory frameworks are established to ensure that, throughout their life cycle, GMOs are restricted to specific conditions or uses that are considered safe for the environment or public health. Any deviation beyond these regulatory boundaries results in the unauthorized presence of a GMO on the market or in the environment. For instance, by trade or transport, a GMO may cross a border between jurisdictions with differences in authorization status or procedures and formally become a UGM (asynchronously authorized GMOs). Furthermore, a GMO may be approved for release into the environment (such as field trials), or for nonfood/nonfeed use, but may unintentionally enter the food or feed chain. Finally, although not very likely, UGMs may intentionally be released when mandatory authorization procedures are bypassed.

Currently, GMO monitoring in the EU occurs in the framework of labeling and traceability legislation. It is essentially organized around routine detection of authorized GMOs in the food and feed chain [19]. In addition, enforcement bodies have a limited policy to monitor UGMs. Efforts to detect UGMs are now principally based on adaptations of routine analytical screening methods: UGMs can be detected by screening for commonly used transgenic elements ["common" regulatory elements such as the *Cauliflower mosaic virus* 35S promoter, or genetically modified (GM) traits shared with known events], in combination with event-specific markers for known, authorized GMOs and/or markers for natural donor organisms. In this indirect approach, the presence of UGMs is inferred when positively detected common markers cannot be explained by the presence of authorized GMOs. Alternatively, in a more direct approach, one could test a number of likely "expected" markers, e.g., markers targeting asynchronously authorized GMOs, that can reasonably be expected to enter the market. However, the choice of "expected" markers is far from obvious, and the list can be virtually unlimited, especially if traits from GMOs in the development pipeline need to be included. Upon detection of a GM-derived analyte, the causative event or events are identified, followed by checking of the authorization status of the particular event in the respective product. However, the potential of analytical testing becomes restricted if information on the genetic modification is limited or lacking. Products carrying genetic modifications that are unknown to authorities, or for which a validated test is not available, are excluded from analytical detection. In addition, owing to sample heterogeneity, it may be difficult to unambiguously identify the causative events, or the product source, on the basis of analytical results alone. Finally, limitations in analytical resources and capacity impose restrictions on the number of products that can be analyzed and the number of different tests that can be performed. As a result, rare and unexpected UGMs may be missed by routine analytical screening strategies.

The knowledge-technology-based exploitation of documentation space: a novel approach to UGM discovery

Here, we propose a novel approach in the way UGMs may be discovered. This approach is based on the collection of documented information on GMO events, and products derived therefrom, during the research, authorization, and commercialization stages.

The first and most fundamental concept underlying the new approach to GMO detection is to recognize that GMOs "lead a life" in two parallel spaces: in physical space and in documentation space. In physical space, a GMO exists as a product in the laboratory, in the environment, or on the market. Clearly, conventional analytical testing is restricted to physical space. In documentation space, dedicated documents are associated with specific steps in the GMO life cycle. Such document collections describe the invention, existence, handling, processing, movement, or location of a particular GMO, like "snapshots" of its physical life cycle (Fig. 1). For instance, a research article reflects the presence of a transgenic line in a laboratory, or a document that describes a field trial reflects the physical presence of plant material on a particular field. Likewise, traceability documents reflect the physical presence of a GMO in a processing factory and/or movement of GMO-derived materials on a trading route. An advertisement pinpoints where a GMO-derived product can be purchased on the market.

The second concept is that knowledge technologies may be used to exploit the documentation space, i.e., to collect, structure, and interpret documented information, and to extract knowledge from it with the purpose of discovering the unauthorized presence of GMOs on the market or in the environment. A model (a schematic, computational representation of a process or system) is used to support the collection, structuring, and understanding of the information. The most obvious model that can be built for the purpose of UGM discovery is a model that covers all aspects of the life cycle of GMOs, including the research, authorization, and commercialization pipelines. Such a general model would reflect a fundamental understanding of common practices in industry and the regulatory

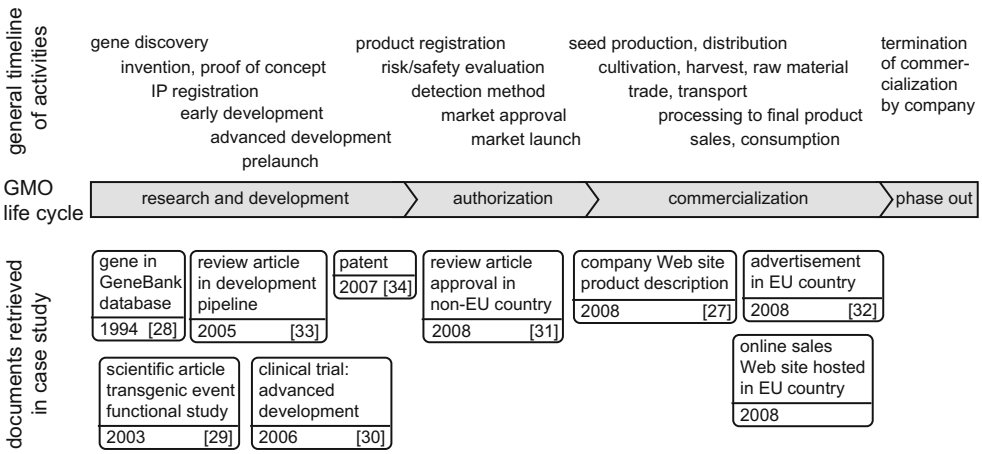

Fig. 1 Simple model describing subsequent steps in the regulated life cycle of a genetically modified organism (*GMO*) and its derived products. In a case study, the model guided a structured Web search for documentation for a particular genetically modified product. Retrieved documents are mapped back onto the life cycle timeline to trace the GMO during research and development, authorization, and commercialization phases, and entry onto the market is signaled by identifying an advertisement and online sales

framework in a given jurisdiction. Since each GMO event has a different history, the general model may contain a collection of *authorized* pathways that may be followed during the life cycle of individual events. The model describes in detail the approved conditions and uses (regulatory boundaries), as well as the different actors and activities involved in the development, authorization, and commercialization pipelines. This model is used in three ways. First, as a mind-map, it guides the search for documented information on GMOs. Second, mapping the retrieved documents back onto the model allows one to trace the pathway of a particular GMO event and the products derived therefrom (Fig. 1) during their life cycle. In turn, documented evidence is used to detect whether these products are handled according to legislation, i.e., to signal if a GMO-derived product exists in a place, at a time, in a condition, or for use, without authorization. Detecting deviations from authorized pathways is at the core of the UGM discovery process. Third, it is used to store knowledge in a structured way.

We distinguish three levels at which document-based information is collected:

1. Event and products derived therefrom. This information describes the (physical) material related to the event: starting from the first transformed material to all materials and products that were derived therefrom. This includes any material that can be sampled, which may be present in the laboratory, in the test field, during commercial cultivation, processing, etc.
2. GM sequence and analytical detection method. This information is related to the definition of the event′s transgene sequence, and the corresponding analytical method used to detect such targets in sampled material.
3. Authorization. This information describes the conditions or uses for which a particular GMO material is considered safe, and for which it is approved. It includes all authorizations necessary during the life cycle of a GMO: for research in the laboratory, field trials or clinical trials, release into the environment, commercialization, etc. Authorizations may differ between jurisdictions.

Using the model to search for UGMs

With use of Web crawling based on a limited list of descriptive keywords that cover each of the GMO events, documentation relating to derived products, actors, activities, etc. is retrieved that can be linked to a particular GMO event, either known or novel to the database. Novel events may be identified in documents containing information on known events (co-occurrence), or by similarity to known events (matching the same descriptive keywords). Web search engines and specialized contextual ranking tools are used to identify the most relevant documents for each event. Advanced text-mining tools may be used to associate documents with a particular event, activity, or actor in the model, and to establish novel links between them. In this way, an event′s progression through the subsequent steps of the life cycle is automatically reconstructed (Fig. 1). Moreover, the status is continually updated as new documents appear.

In parallel, queries are designed that systematically check, at critical points of the life cycle, that the condition or use of a GMO complies with the relevant authorization. For example, an advertisement for a GMO-derived product signals marketing in a given country, and marketing requires authorization for commercialization in that particular jurisdiction. So, a query is designed that automatically connects both documents in the database, and signals if such an authorization dossier is missing. The UGM discovery process is typically iterative. As the results of the initial searches are mapped onto the model, the network is refined by incorporating unforeseen new sources of data

or information. This, in turn, allows the querying process to be improved. The entire process repeatedly collects evidence to build a case around suspect products and generates alerts.

In retrospect, most reported UGM incidents were initially discovered by manual inspection of documentation on products, some of it readily available in the public knowledge domain, rather than during routine analytical screening. In several independent cases, detailed analyses of global trading records revealed that GMO products were imported into regions where they were not authorized, and that they were only later confirmed by molecular analysis [8, 12, 13, 18]. In this way, unauthorized imports of GM papaya from Hawaii were discovered by the Bavarian enforcement authorities. Although the underlying discovery process may be complex, the logic behind the discovery of recent UGM cases (Table 1) can be understood and translated into a structured, systematic search action for similar cases. The structured searches embedded in the model may be used to answer two types of questions:

1. Given a list of GMOs in the development pipeline (e.g., [24, 25]), can we trace their subsequent development as new documents appear?
2. Given a set of real-life scenarios that have already led to unauthorized presence on the market (Table 1), is there a particular novel GMO that follows the same pathway?

Importantly, since the model collects information across all stages of the GMO life cycle, including stages prior to approval for commercialization, the approach is not limited to tracing asynchronously authorized products.

Knowledge technology supports the search process

So far, cases of UGM discovery have been the result of the explicit awareness and initiative of individual institutions. UGM discovery is likely to remain incidental, unless experts are better supported in their continual, highly manual task of searching and linking relevant information. Fortunately, the challenge of knowledge integration in the life sciences, which also applies to the UGM discovery process, has been recognized by computer scientists. Although UGM discovery will require human supervision, many of the tasks relating to data retrieval, filtering, and (to some level) interpretation can be automated. This is the research area of data mining, text mining and other knowledge technologies aimed at knowledge discovery from various large information sources, including those available on the Web. For instance, the Joint Research Centre of the European Commission has set up a Web mining and intelligence real-time media monitoring system (European Media Monitor) that scans thousands of news sources, classifies articles in 43 languages, and alerts and informs users about their topics of interest [26]. This system currently retrieves all articles from key news portals for a list of defined topics (such as "GMO"), but does not allow fully customized searches. It may classify articles according to content, but it does not make use of a high-resolution classification scheme, such as the GMO life cycle model. Therefore, it is currently not fit for reiterative, investigative searches nor for the detailed mapping of retrieved documents onto the model, which is required to trace individual events. All these actions are currently performed manually case-by-case by human experts. Open source intelligence is a form of intelligence collection management used by governments, intelligence agencies, the military, academia, and business. It aims to provide a solution to the virtually impossible task to manually process thousands of documents by developing tools that automate the process, both in the retrieval of documents and in the extraction of information and in representing the information in a meaningful way.

Tracing products in documentation space: a case study

To illustrate that GMO events can be traced in documentation space, a Web-based search for EU companies with potential novel GMO-derived products in their pipeline was carried out. The product Coban was selected as a case study. Coban tablets contain recombinant human intrinsic factor (rhIF) collected from dried, powdered transgenic *Arabidopsis* leaves and vitamin B_{12}, and are intended for patients suffering from vitamin B_{12} deficiency [27]. Next, in several iterative searches, associated documents were collected with the Web search engine Google, using keywords such as product and company name, rhIF, and transgenic *Arabidopsis*. Several lines of evidence were reconstructed in parallel: one examining whether the product was present on the market, one examining the authorization status, and one compiling information on the transgene sequence of the GM event, required for analytical confirmation. Each search result was manually processed by examining the top 25–50 hits and interpreting the most relevant documents in detail. In some cases the investigation was refined by using more specific keywords. Selected documents were then associated with specific, subsequent steps in the product life cycle by matching the content of the document to a specific activity in the research, authorization, or commercialization phase (Fig. 1) [27–34]. Various actors (i.e. the research institute, the company that developed the GMO, authorizing bodies, the producer, the distributor, etc.), activities, and links between them were identified. The documents were retrieved from the Web space covered by the Google search engine. The types of documents that were examined are highly heterogeneous,

including Web sites, technical scientific publications, scientific reviews, DNA sequence databases, a patent, regulatory documents, an advertisement, and Web sites hosting online sales indicating that the product was commercially available. The identity of the product was confirmed by molecular analysis [17] using information on the genetic modification obtained during this search.

This case clearly shows that it is possible to trace products in documentation space, independent of analytical screening. In this case, all necessary information to identify the product, to locate it on the market, and to design an analytical test was publicly available through the Web. Importantly, although the Web search represents one example to address the documentation space, the documentation space need not be limited to the Web. For instance, a competent body may expand the documentation space by exploiting all (including confidential) information obtained directly from industry, governments, or from other competent bodies worldwide. Several institutions have been established to support the flow of information between governments and industry. For instance, the Biosafety Clearing-House is a mechanism set up by the Cartagena Protocol on Biosafety to facilitate the exchange of information on living modified organisms. Global access to a variety of scientific, technical, environmental, legal, and capacity-building information is provided. In addition, various authorities worldwide provide information on authorizations and/or field trials [35–39].

Complementation of analytical strategies for UGM detection

This case study further illustrates that if such analysis is systematically performed for all GMO events that exist, a comprehensive and continuously updated overview may be obtained that describes (1) which products exist, and at which stage during their life cycle, (2) which ones are approaching the market or may be released into the environment, (3) which products are not handled according to regulations and may be subject to dedicated sampling schemes, and (4) which methods may need to be developed to allow for analytical detection of all relevant events (screening platform optimization). As such, this system may represent an important monitoring tool to complement the current analytical GMO detection platform. The information obtained may be used to support the two main aspects of analytical detection: the choice of targets to be detected and the choice of products to be sampled [17].

The novel approach may support the analyte-centered approach by defining the choice of targets. The cost and complexity of analytical screening will continue to increase, owing to considerable diversification of biotechnology traits on global markets [21, 22, 24, 25]. Two types of cost are associated with this trend. First, the cost of development and validation of each new test (development cost). Second, the cost of analyzing a particular product with any or all of these tests (operational costs). The current analytical screening platform inevitably needs to be expanded with tests for the novel traits to maintain its potential to detect novel UGMs. The documentation-based approach will help to manage the development cost by finding new targets, and by identifying and/or prioritizing the UGM events (traits) that are the most likely to enter the market. Furthermore, information of the GMO content of products can guide the choice of analytical tests to be performed for a given sample, and thus reducing operational costs.

Limitations in analytical resources and capacity mean that only a small percentage of all products are actually sampled. To avoid random sampling and consequent low detection probability for rare UGM events, information on the GMO composition of products must be used to enrich the testing laboratories with potential UGM-containing samples. In some cases, traceability records are used to design sampling schemes for product types with higher risk. In addition, sampling schemes may be adjusted after a UGM alert, to monitor the spreading of a novel UGM product. Nevertheless, the initial discovery itself (i.e., what happens just prior to the official UGM alert) will become the critical factor in preventing or minimizing consumers′ exposure to UGMs, and documented evidence may support this step. However, if the volume of documents becomes too large to be manually handled by an inspector, the information will remain unused even if it is available, and

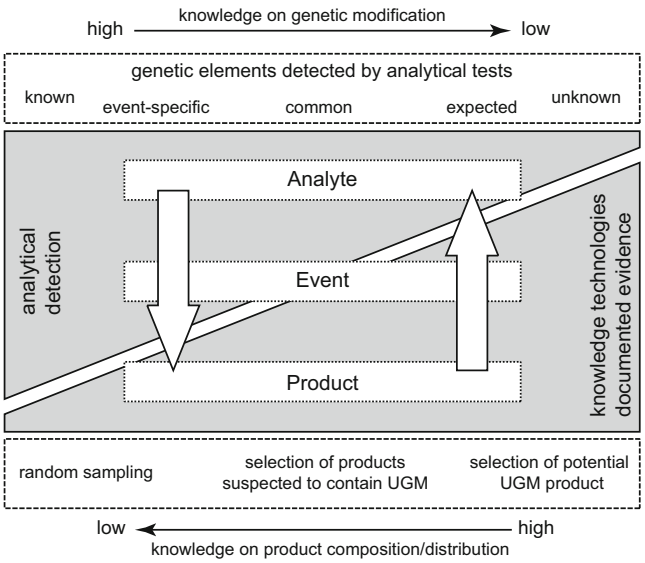

Fig. 2 Two complementary approaches: "analyte-centered" and "product-centered" are necessary to discover unauthorized GMOs (*UGM*)

novel unknown UGMs may be missed. The purpose of the knowledge-technology-based approach is to vastly expand the volume of information that can be exploited and to structure the complex, investigative search.

Currently, routine GMO screening is performed using an "analyte-centered" approach. This approach starts with the detection of a GMO-derived analyte, followed by identification of the events present in the sample, and establishment of the authorization status of the product (Fig. 2). An alternative "product-centered" approach, as proposed here, works in the reverse order. First, the product-centered approach collects documented information on the presence and distribution of GMO-derived products on the market. Next, it identifies GMO-derived products that do not comply with authorization. At the same time, GM trait sequence information is collected to support analytical testing. Finally, the product is located on the market and sampled for event-specific analytical confirmation. The Coban case is a clear example of a product-centered approach: using documented information for product selection followed by analytical confirmation of product identity. So, depending on the available information, a choice between the analyte-centered approach and the product-centered approach can be made on a case-by-case basis [17].

The way forward: enhancing discovery capacity to limit the risks

UGM discovery capacity is crucial to limit the risks associated with UGMs, both in curative and in preventive ways. First, early discovery limits spreading, thus restricting public or environmental exposure to UGMs. Second, identifying major causes of UGM release allows for measures that to prevent repetition and suppresses the frequency of occurrence. Third, intentional release of UGMs is discouraged if powerful strategies ensure a high rate of discovery and consequent legal action. A solution should not only focus on the improvement of analytical detection technology, but should also benefit from recent and future developments in knowledge technologies, which are better suited for true discovery purposes. The new documentation-based strategy proposed here has many benefits. It enhances market coverage, reduces discovery time, focuses attention on an informed, targeted selection of suspect products for dedicated analytical confirmation, and consequently ensures efficient use of analytical resources. Nevertheless, documented evidence of a suspected UGM must still be confirmed by independent experimental evidence. Molecular information on the UGM trait collected during the discovery process will guide the design of an appropriate detection method. Clearly, the documentation-based approach is limited to instances of UGMs that are recorded. For instance, if a company is not aware of contamination, there will be no documentation available to trace it, and routine analytical screening may be the only alternative. Hence, both discovery and detection technologies should be further developed in parallel for their respective and complementary purposes so that the capacity to discover various classes of UGMs is balanced with their risk. A concerted action is required to address the problems posed by UGMs, and applies to legislations worldwide. A novel discovery system can only be established through close collaboration between fundamental research on knowledge technologies, competent authorities, GMO enforcement bodies, and industry. A computational framework should be established that encompasses the modeling of the GMO life cycle, and allows to perform investigative searches using highly heterogeneous information sources. It should also contain a user-friendly interface, so that the system can be adapted to the specific needs (tailored models and specific queries) of different end users, including competent authorities and GMO enforcement bodies, and also research organizations, industry, NGOs, and public services.

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