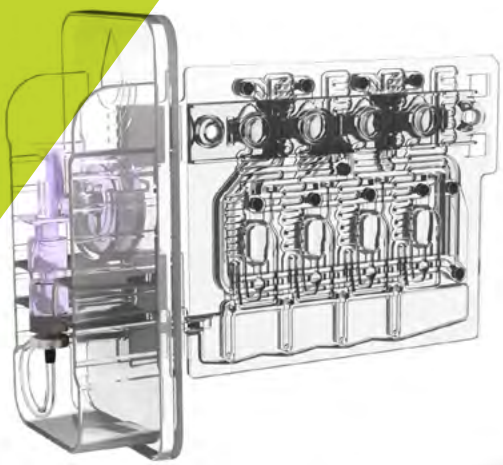


# A Framework for Evaluating Assays for Automation —

## Understanding Risks, Tradeoffs, and Prioritization in Your Next Automated Assay Development Program

key tech

# A Framework for Evaluating Assays for Automation —

## Understanding Risks, Tradeoffs, and Prioritization in Your Next Automated Assay Development Program

A diagnostic assay must be examined from all angles to create a foundation for end-to-end product development and successful commercial launch. This framework outlines a systems approach and presents a series of lenses to apply when evaluating assays for automation. The process identifies risks, defines constraints, and outlines a de-risking program as the first step toward commercialization.

**Product Strategy**

**Ease of Use**

**Sensitivity Analysis**

**Consumable/ Durable Interface**

**Reagent Handling**

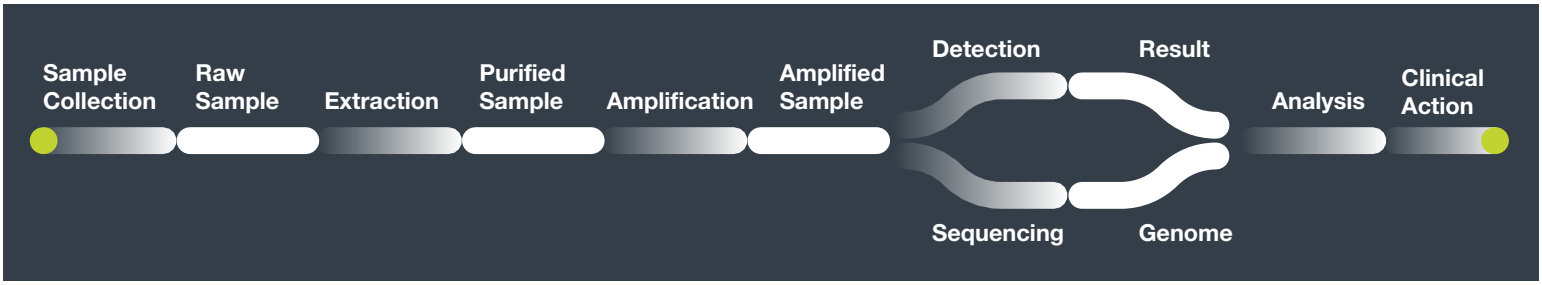
**Fluidic Control**

**Temperature Management**

**Algorithm Development**

**Tech De-Risking Methods**

**Scale**



LENS 1

# Product Strategy

It is essential to start with the overarching product strategy, which acts as a frame of reference to guide decision-making throughout development.

Initial strategy is informed by market and competitor research, conducted to define requirements for the product.The purpose here is to work backwards from the commercial goal, to understand the key drivers of product architecture, and to identify where the technical risk lies. Of the many product strategy considerations, here are two key drivers: The intended price target and the intended use cases.

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The price target will drive unit and consumable architectures, and prompt focused questions related to where the costs can be trimmed. Critical components such as automation subsystems or detection modules should be evaluated from a cost perspective to make sure unit costs at volume will meet price targets.

The setting the device will be used in, along with the intended end user, drives strategic development. If the product is intended to be used at home by an untrained user, the evaluation of the assay and potential risks will be more rigorous than if the device is used in a clinic by trained clinicians. In a remote environment, the device may need to be handheld or environmental factors may require more stringent design tactics and development testing. A clinic environment would be much more controlled.

When developing a next-gen product, the original product should be considered first. What went well from a product strategy perspective during the planning, development, launch, and maintenance of that product? What problem areas can be improved in the next-gen product? What can we learn from the original product to improve overall safety, efficacy, and reliability for the new device?

Most importantly, a good product strategy must determine where the value lies in the development of an automated platform. It may seem appealing to offer a sample-to-answer product, but a shrewd product strategy may dictate a more focused approach: Perhaps there is value in focusing solely on a novel detection technology, and leaving the sample preparation and amplification for existing products on the market. A product that does one thing well may be better than a full-featured product with a delayed launch due to an overly ambitious development effort.

LENS 2

# Ease of Use

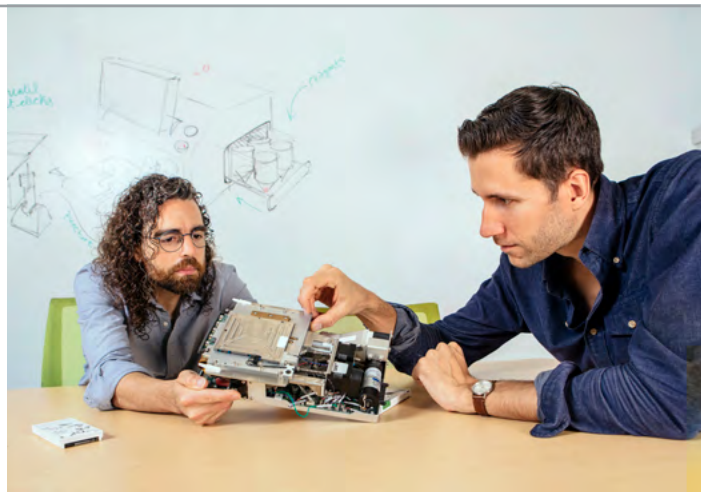
An ease of use lens will identify which areas of the eventual product are most valuable to automate, and which are better left as manual user steps. Simplifying user interaction and minimizing potential human error is the goal, but not every step can be automated - nor should it. This lens helps identify the risks and tradeoffs between the complexity of automation and the likelihood of human error.

How realistic is the ideal use case? Which assay steps are the most difficult or complex to fully automate? Are they better left as manual user steps? What are the limitations of existing technology? If the goal is to have a completely automated sample-in, result-out platform, i.e. a CLIA-waived user experience, it's critical to understand the human element.

Sample collection and loading are generally the main risk factors. For more complex assays, where there is more than one sample to load or where the sensitivity analysis and key requirements necessitate high precision, it is critical to assess how users would interact with a device. This assessment can be performed using a non-functional, "looks like" prototype that a user can interact with. This type of test allows the team to understand workflow cues and accessibility challenges, in addition to developing wireframes of the intended user interface to observe how users navigate them.

LENS 3

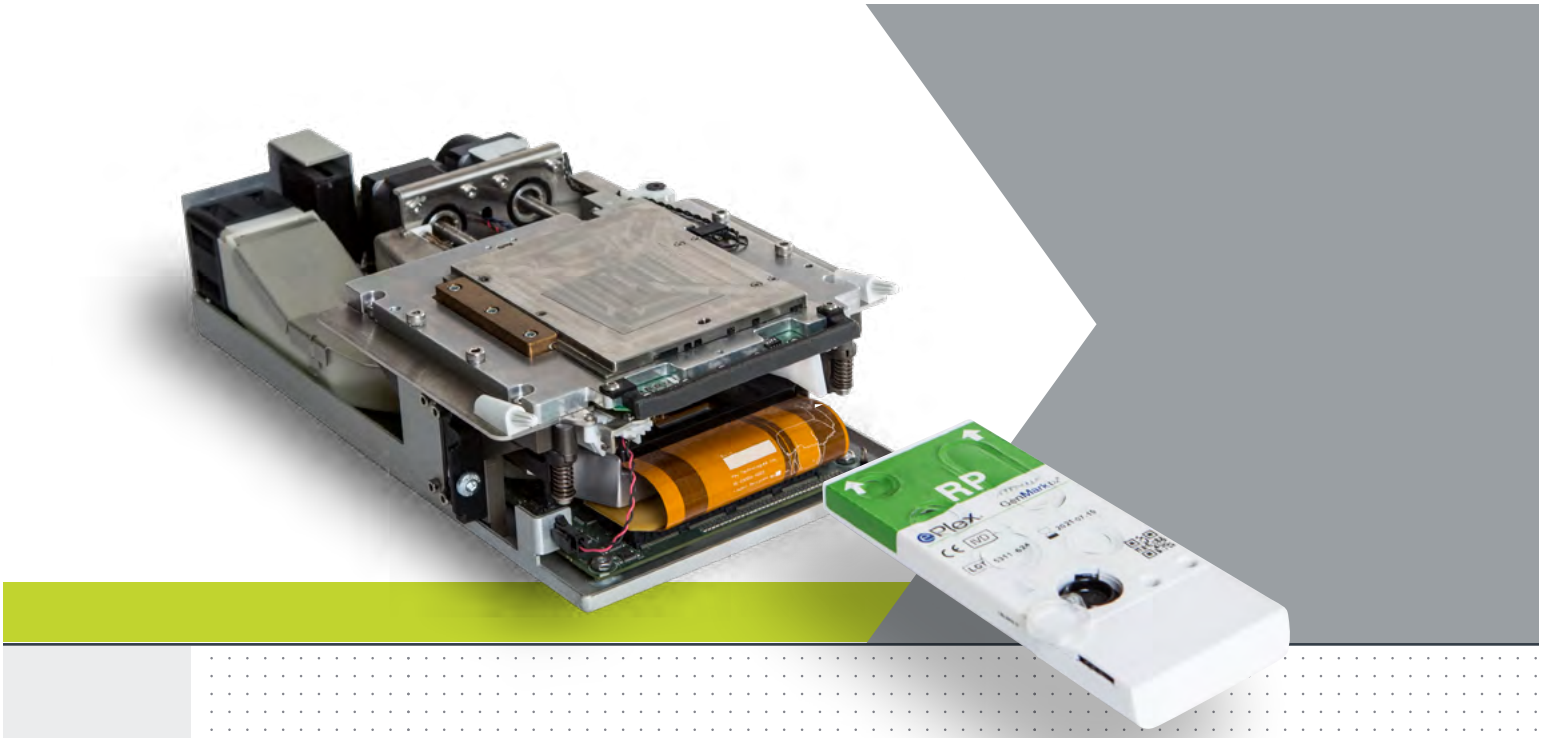
# Sensitivity Analysis



Acceptable ranges for volume, temperature, etc. must be determined for each assay step. Is the assay sensitive to volumetric or thermal variation? How closely interdependent are two sequential assay steps?

This analysis allows the engineering team to know what variables need further studying in order to accurately assess technical risk.

In general, the less sensitive an assay, the easier and more cost-effective it will be to automate. Don't forget to consider external factors during this analysis. If the device is used in a lab, environmental factors may be minimal, but if the device is in the field, things like sunlight, dust in the air, daytime temperature, or even the pressure change from something as simple as a door opening or closing can all impact assay performance.




LENS 4

# Consumable/Durable Interface

Here, the focus is on device functionality and where features will reside in the system: What belongs on the cartridge and what belongs on the instrument to achieve performance and system requirements?

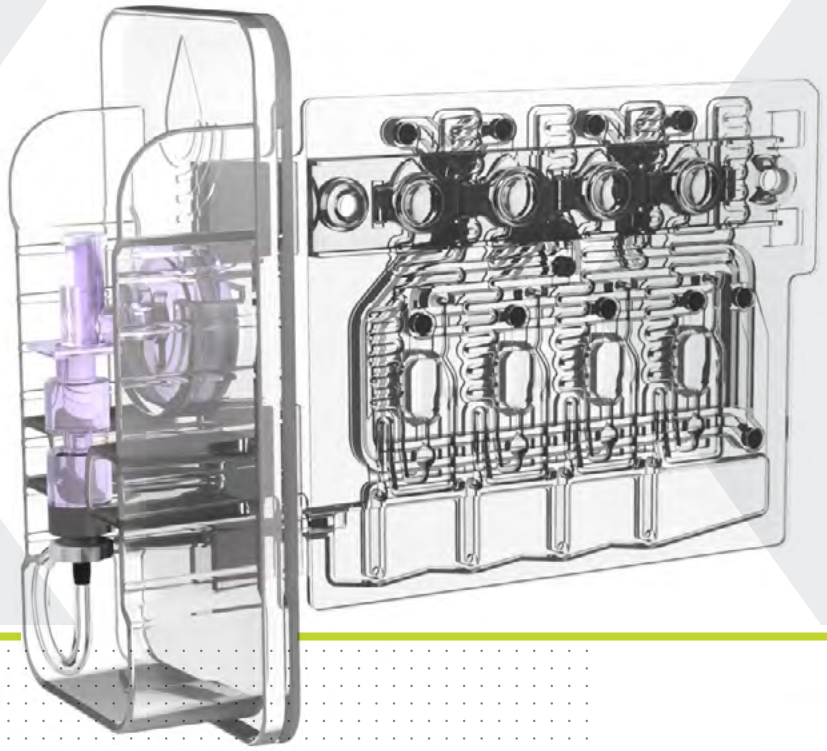
A lot of the interface definition is driven by consumable cost targets, then the assay is quickly evaluated from a technical perspective: What type of sample is it? How is it collected and stored? What is the sequencing or detection target? How does the sample need to be manipulated to get clinical results? How is temperature being applied to the consumable? If the device will be in the lab or the field, how is the temperature being managed? Does the assay require chemical or mechanical lysis? How will the consumable or durable allow for proper temperature control?

> What belongs on the cartridge and what belongs on the instrument?

The answers to these questions will drive de-risking experimentation, cartridge cost, instrument complexity, and maintenance requirements, depending on how the interfaces' functions are allocated between cartridge and instrument.

There are trade-offs between cost and simplicity. For example, if you are trying to break up blood cells on a cartridge, the mixing mechanism is a key decision point. Do you have a rotor that spins on the consumable side with mechanical interfaces to allow a motor on the instrument to drive it? Or is there a low-cost motor on the cartridge itself, with a cleaner electrical interface to the instrument? This choice presents a tradeoff between interface complexity and consumable cost.

Sonication can also be addressed with this consumable-durable view. Sonication gives you a cleaner interface - just a chamber on the consumable - at the expense of a more complex instrument.



LENS 5

# Reagent Storage and Handling

Continuing along the same vein, it is important to address whether reagents belong on the cartridge or the instrument. The main question is how those reagents will be introduced to the assay: through durable containers on the instrument, which will be used for hundreds of runs and replenished as part of scheduled maintenance, or in small doses located on the consumable?

Additionally, different reagents require unique treatments. A lyophilized, or dehydrated, reagent must be stored and handled differently than a wet reagent.

Reagent handling often dictates high-level architecture decisions, so addressing these details early facilitates a better overall product architecture.

There are several significant considerations for reagent handling:

**Cost**

If consumable cost is a significant driver, putting as much on the instrument as possible keeps the cartridge cost-effective.

**Volume**

The same principle rings true if there is a large reagent volume; the cartridge can only reasonably store so much.

**Maintenance**

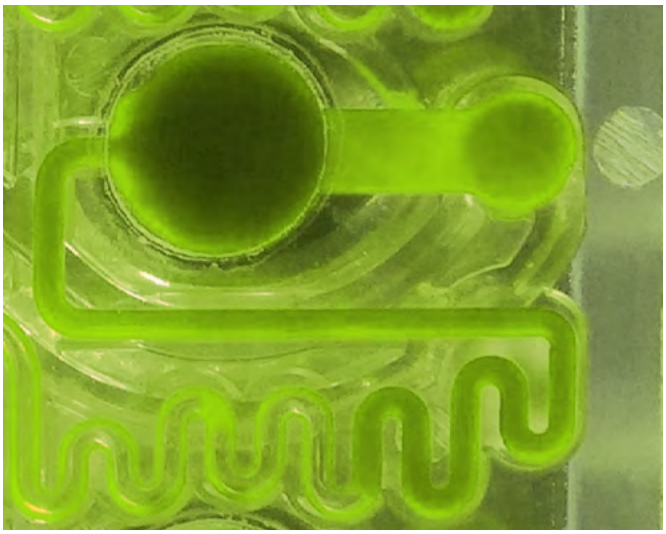
If the reagents are located on the instrument, their containers will need to be refilled and cleaned during routine maintenance.

**Stability**

Reagents come in different forms, which means they will have different shelf lives and different sensitivities to environmental factors, particularly during storage.

LENS 6

# Fluidic Control



Precise liquid handling is a core challenge in assay automation. How will liquids, and typically air be controlled in a reliable, repeatable way?

When working at a microfluidic scale, it's important to understand the fluid's properties, such as viscosity and surface tension. Will the viscous liquid lose residue as it is pushed along a channel? Is that a problem?

It's also important to consider whether the fluid is really a simple fluid at all: For example, although we commonly think of blood as a liquid, in practice it is jam-packed with solids, and will often behave more like a pile of small objects than a true liquid. The same can be said for a sample full of paramagnetic beads. These fluid properties have significant implications for the determination of a good fluidic control scheme.

The type of fluidics control methods the product may use is also important to consider. Pipetting requires a different automation solution than using a rotary valve or a traditional pump, for example.

Contamination sensitivity also needs to be addressed, ensuring sample splatter is contained and safeguarding against amplicon contamination and false positives.


LENS 7

# Temperature Management

By understanding the effects of temperature on the instrument, cartridge, and assay performance, effective methods can be developed for measuring and controlling temperature.

Depending on the assay requirements, the calibration or control schemes will be more or less challenging. Generally, temperature control accuracies of about ±1°C can be attained with simple, conventional methods. If tighter accuracy is required, then the product will need more creative or sophisticated temperature measurement techniques, such as calibration of each temperature measurement element, in-fluid temperature control, or double-sided heating elements.

These challenges can trickle down to other components on the cartridge or instrument; will condensation, evaporation, or humidity impact the reagents? How fast do PCR cycles need to be performed? Might ramp rates be hindered by larger fluid volumes? How tightly does temperature need to be controlled during DNA hybridization?

It all goes back to those trade-offs. All of these factors can generally be managed, but at what cost?

For example, how you build the thermal geometry matters so that you can ramp fluids through temperatures quickly and accurately.

There is also the science to think about:

**Enzyme Activity**

Does a specific temperature need to be reached to incubate enzymes, such as Proteinase K, to help to break down proteins in the lyophilization process?

**Target extraction and Elution**

Is there a certain temperature that needs to be reached and held to facilitate DNA capture from the sample? How is the chamber or reservoir going to maintain temperature? Is there a specific temperature needed for elution to occur successfully?

**Ramp rates**

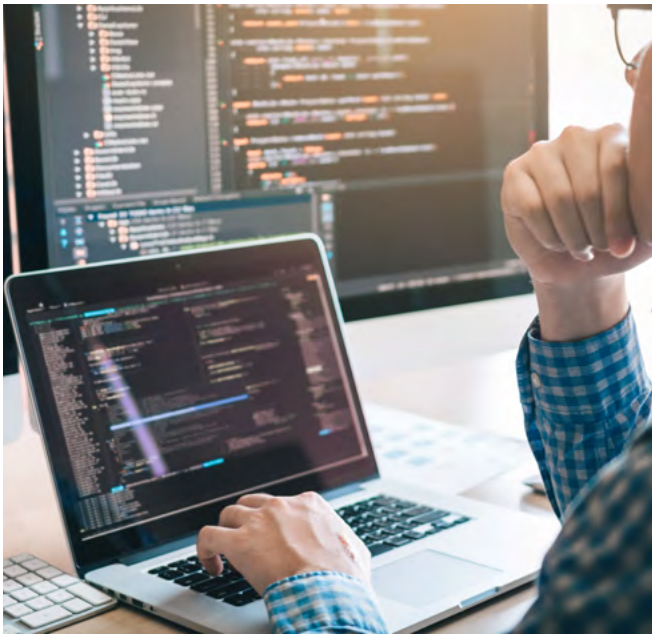
How quickly can temperatures be cycled in PCR regions? Consider what may be limiting those ramp rates: high fluid volume, limited instrument power, etc.

**Hybridization temperature**

Hybridization is a strand of DNA bonding to another single strand. This requires a specific range of temperatures in order to occur and the longer the DNA sequence, the tighter the temperature control required.

LENS 8

# Algorithm Development



The data processing algorithm is often the core value proposition and differentiator being brought to market. Two factors ensure it produces a clinically actionable diagnostic result:

1. **Understanding the limits and constraints of the algorithm.** How much data needs to be acquired and stored? What are you doing with the raw data to turn it into a result? How intensive is the algorithm from a data processing standpoint? What are the sensitivities of the algorithm?

2. **Recognizing the instrument requirements that the algorithm demands.** How big does the processor need to be? How much storage is needed? How challenging is it to design the electrical system and software architecture to accommodate the algorithm? How long are you going to need to store the results? Can data processing be performed off-instrument? Understanding the sensitivity and specificity of the algorithm can also help to avoid false negatives and false positives.

Often the algorithm has already been tested. Yet, until the parameters of those tests are understood, the data can't be reproduced or optimized to the actual use case environment. For example, if the algorithm was developed in a lab, it will react much differently with the assay in an uncontrolled environment. This requires further investigation early in development.

Additionally, understanding the sample that was used when the algorithm was developed is also critical. If blood was used, was it actual blood? What kind of blood? Asking these questions allows IVD development teams to determine how real the measurement is, taken out of a lab setting.

Weighing the costs and benefits of complex algorithms is essential in the process of IVD development.

Take genomic sequencing, for example. One algorithm can generate terabytes of data, which must be stored, processed, and transmitted. A more expensive and complex system may process the algorithm and data more quickly, while something that is low-cost with a smaller processor may take hours or days longer. As the core market differentiator, the algorithm's speed among the competition is a key consideration.

LENS 9

## Tech De-Risking Methods

Identifying what risks need to be mitigated and where various de-risking methods should be deployed is also essential. Finding the most effective methods, such as prototyping a portion of the assay steps, developing an analytical model of a physical process, or running a computer simulation, are ways to do this.

Options include:

1. **Creating testbeds**
   Eliminate time-consuming tests and save money by vetting subsystem risks using the above lenses. Once you have narrowed these risks down, testbeds can be used to find answers to key questions before product development starts.

2. **Modeling and simulation**
   Mathematical modeling can allow the team to understand the fundamental principles of the assay and to explore the solution space analytically. Other tools, such as FEA, can be used to explore design tradeoffs before prototyping to validate the model.

3. **Subcomponent specialist consulting**
   Work with a specialist to understand performance specifications. For example, if you're working with a lyophilized reagent vendor, they should be able to relay information about humidity requirements for their product.

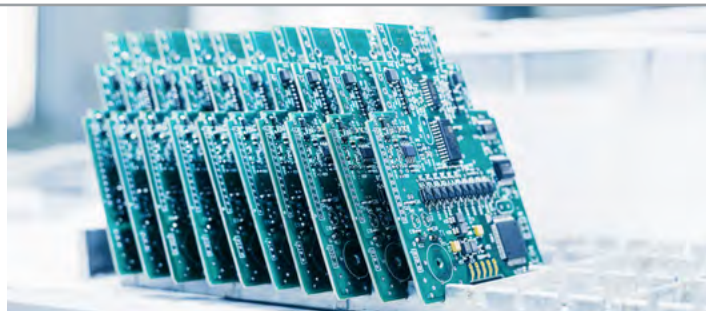
LENS 10

## Scale

The final lens, and the bookend of this framework, is scale. How do you know how reliable your product is after launch? How are you collecting feedback on your product? How will you identify and understand instrument or assay failures? How will you adapt your preventative maintenance program to address these issues?

At this point in the process, the impacts of high quantities and long-term use on the instrument and cartridge reliability, cost, and performance should be considered. There should be a good understanding of whether the device can work in large numbers and what strategies should be employed during development to improve reliability and performance while containing manufacturing and maintenance costs.

Keeping these considerations in mind should ease the selection of your manufacturing partner. The right partner will understand device complexities and help you develop a plan for producing the product at the desired scale.



## Two Decades of Success

Key Tech is proud to have spent the last two decades partnering with clients to tackle tough product development challenges and create successful in-vitro diagnostic (IVD) products that make a difference. Transforming complex technologies into intuitive products is where we thrive, and this framework can help facilitate a successful assay automation program. So tell us, what is your product development challenge and how can we help?

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Let's Talk About
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