Received: 7 December 2025 | Revised: 23 January 2026 | Accepted: 6 February 2026 | Published online: 28 February 2026

REVIEW

Smart Wearable Technology
2026, Vol. 00(00) 1–7
DOI: 10.47852/bonviewSWT62028721

Biosensors for IgG Identification in the Absence of Infection to Isolate Autoimmune Activity

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Abstract: People living with chronic autoimmune conditions could run the risk of misdiagnosis. This study involved a systematic review of literature examining how elevated autoimmune-prevalent immunoglobulin G (IgG) coincides with average or low procalcitonin (PCT) levels and normal lymphocyte and neutrophil levels, which can indicate autoimmunity versus bacterial infection or viral infection, respectively. The study results showed a trend in cases where high IgG levels, despite normal PCT and lymphocytes/neutrophils, were concurrent in people with autoimmune disease, alongside a gap in research surrounding how wearable devices could be used to measure IgG against the presence or absence of indicators of acute infection. These findings helped inform the need for a rudimentary algorithm for a wearable biosensor to identify excess IgG in the presence of baseline or low levels of PCT and normal levels of lymphocytes and neutrophils in the blood serum. This device would theoretically aid in differentiating autoimmune conditions from active infection.

Keywords: biosensors, autoimmunity, immunotherapy, personalized medicine, functional medicine

1. Introduction

Stigma against individuals with less easily diagnosable autoimmune chronic illnesses presents a detriment to the treatment of such conditions. Brain–gut disorders such as irritable bowel syndrome are a good example of incorrect psychiatric diagnosis, often leading to unhelpful and sometimes harmful prescribed medication while the underlying disease goes untreated [1]. However, despite these symptoms often being written off as psychosomatic due to diagnostic difficulties, the belittlement itself often harms the patient's psychological well-being rather than the other way around [2]. Given the increased global prevalence of autoimmune chronic conditions following the COVID-19 pandemic, artificial intelligence (AI)-based wearable solutions for more conveniently identifying autoimmune disorders could be beneficial for differentiating these conditions from infection and psychiatric ailments toward improved personalized care [3].

While a previous study from 2015 explored the onset chronology of comorbid physiological and psychiatric conditions, the study focused only on a certain age group and did not involve any technological solution to aid in diagnosis [4]. Meanwhile, the present study analyzes the most recent literature to assess trends in IgG prevalence in individuals without acute infection. Such trends would hypothetically help inform the parameters for an AI-equipped wearable identification system for potential chronic autoimmune activity where no apparent infection exists.

Physical chronic illness has already been cited as a factor leading to anxiety and depression for many individuals due to the decrease in quality of life [5]. Notwithstanding, plenty of studies adhere to mental health as a root cause for chronic physical conditions, which risks patient dismissal and inappropriate medication prescription [6].

This study aims to assess the presence of immunoglobulin G (IgG)—indicating low-grade inflammation—across various autoimmune conditions as a potential chemical source of inflammatory symptoms that could be targetable by an algorithm designed to isolate cases of elevated IgG in the absence of legitimate infection. As such, this review begins with an assessment of literature covering the biomarkers for differentiation between autoimmunity and infection, followed by existing studies on wearable technology solutions for analyzing these biomarkers.

2. Literature Review

The literature review covered several studies, each for bacterial and viral infection differentiation from autoimmune disease. These studies drew largely from the National Institutes of Health in the areas of autoimmunity, immunology, and molecular sciences. The articles were published within the 2021–2025 timeframe and examined trends in the concurrence of elevated IgG and average or low PCT in individuals with autoimmune conditions (bacterial infection) and high lymphocyte or low neutrophil counts in the presence of elevated IgG (viral infection). The primary keywords used were "autoimmune disease," "immunology," "biosensors," and "infectious disease." The specific autoimmune conditions included were acute fever presentation in autoimmune

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patients, rheumatoid arthritis, autoimmune glial fibrillary acidic protein astrocytopathy misdiagnosed as intracranial infectious disease, and the Epstein–Barr virus relationship with autoimmunity. The attention to elevated IgG served as a control for the differential algorithmic solution for the proposed wearable device. Finally, PCT, lymphocytes, and neutrophils were considered as potential differentiators between autoimmunity and infection [7]. While elevated IgG can occur due to conditions other than autoimmune disease, the marker is used here as a foundation alongside routine markers used to assess for infection for a holistic viewpoint.

2.1. Bacterial infection

Distinguishing disease flare from acute infection in febrile patients known to have autoimmune conditions can present a challenge [8]. This study evaluated the usefulness of procalcitonin (PCT) and other common inflammatory biomarkers in differentiating disease flare from bacterial infections in the emergency department (ED). In a cross-sectional observational retrospective study, Covino et al. [8] examined consecutive febrile patients with an established diagnosis of systemic autoimmune disease who were hospitalized following ED admission. PCT proved the best method for differentiating flare from infection, compared to white blood cell count and C-reactive protein (CRP).

Hereby, Covino highlighted the efficacy of using PCT levels to distinguish between bacterial infection and autoimmune flare as the root cause of acute fever. However, this study did not specify immunoglobulin as a biomarker due to the fact that the individuals involved were already diagnosed with an autoimmune disorder, nor was the usefulness of a wearable biosensor discussed for measuring biomarkers in the ER.

In the next study, Chen et al. [9] used serum PCT and CRP levels as diagnostic markers to distinguish between bacterial infections and flares in systemic lupus erythematosus (SLE).

Fifteen studies were included in the analysis [9]. Serum PCT and CRP levels were significantly higher in SLE patients with bacterial infections compared to SLE patients with flares. However, once again, the subjects in this study were not examined within the context of using PCT or CRP versus IgG to differentiate between lupus flare and acute infection, nor was a wearable device solution considered for differentiation support.

In the next study, Huang et al. [10] found that PCT could act as an essential biomarker for diverse clinical contexts, including sepsis diagnosis in EDs [10]. They also noted PCT applications as including the identification of pathogens, infection severity assessment, ensuring appropriate drug administration, and theranostic strategy implementation.

However, current clinical methods cannot accurately monitor PCT in real time. Therefore, this review examined emerging PCT immunoassay technologies for improving detection performances, such as ease of operation and high precision. The fundamental principles of the best methods were covered first, including chemiluminescence, colloidal gold immunochromatography, immunofluorescence, latex-enhanced turbidity, enzyme-linked immunosorbent, and radioimmunoassay. Then, improved methods using new materials and new technologies were detailed, such as merging with responsive nanomaterials, Raman spectroscopy, and digital microfluidics. Finally, the detection performance parameters and clinical significance of PCT detection were also reviewed.

As in the previous studies, while Huang et al. discussed the ability of immunoassay detection to identify IgG in lower amounts than other methods, they did not explore how IgG levels could be compared against PCT levels for the purpose of autoimmune conditions. As with the other studies referenced thus far, a wearable solution for real-time biomarker monitoring was not considered.

2.2. Viral infection

On the viral infection front, Berger et al. [11] reported that reduced lymphocyte counts in peripheral blood are one of the most common observations in acute viral infection, despite the also common phenomenon wherein viral infection increases lymphocyte count. While many studies have already examined the impact of immune (dys)regulation during SARS-CoV-2 infection, the long-term consequences for lymphocyte homeostasis are less clear.

Berger conducted a retrospective analysis of flow cytometric data from lymphocyte subpopulations in 106 patients with confirmed SARS-CoV-2 infection who received medical care at their institution. Significant differences between post-COVID-19 condition (PCC) and COVID-19 convalescents compared to UHC were observed in T helper cells and class-switched B cells. However, Berger did not detect specific or long-lasting immune cellular changes in PCC compared to the non-PCC.

Thereby, while this study assessed the pressing matter of long-term effects from COVID-19, IgG as a sign of long-term autoimmunity did not surface as a differential method. Rather, the study only reports a decrease in IgG, which—along with increased IgG—can potentially suggest chronic illness. Once more, a biosensor device could be used to assess real-time changes in IgG levels following COVID-19 infection.

Meanwhile, Sundaresan et al. [12] reported on research indicating that several methods such as molecular mimicry, epitope spreading, and bystander activation, can lead to viral-induced autoimmunity. This study reviewed the latest insights into the pathomechanisms of viral-induced autoimmune diseases (AIDs) and assessed recent findings on COVID-19 infections and the development of AIDs. Therefore, while the present study uses high lymphocyte count as a general potential indicator of viral infection, it is important to keep in mind that the opposite can also occur.

2.2.1. Wearable devices for biomarker monitoring

Sempionatto et al. [13] presented their literature review of current and future uses for wearable biosensors for general personalized medicine. They cover how, for biomarker analysis specifically, wearables could be helpful due to their being noninvasive. These sensors are often implemented into accessories and clothing to measure biomarkers such as heart rate, glucose levels, and hydration status. Recent innovations in downsizing, materials science, and wireless communication have made wearable biosensors more accessible, comfortable, and of higher functional quality. This review presented a general summation of wearable biosensor technology, with an emphasis on advances in sensor design, data analysis algorithms, and fabrication techniques. Like the present study, Sempionatto explored the use of wearable technology in not only well-known areas such as fitness but also disease diagnosis. Finally, this review also considered the future of wearable biosensors in healthcare and wellness by summarizing existing trends and novel breakthroughs.

However, despite the focus on chronic illness monitoring, this study did not highlight specific relevant biomarkers for differentiation.

On the topic of using biosensors for IgG detection specifically to help isolate autoimmunity, Teniou et al. [14] performed the closest review in this area. This study reported that conventional diagnostic methods for autoimmune diseases require tedious sample preparation, sophisticated instruments, a dedicated laboratory, and qualified personnel. Biosensors were designated as the optimal tool in clinical analysis for an early diagnosis due to their high sensitivity, simplicity, affordability, possible miniaturization through point-of-care testing (POCT), and potential ability for real-time analysis. This review covered the most recently developed biosensors for autoimmune disease detection as well as the associated biomarkers. The first part of the review focused on the biomarkers targeted for isolating autoimmune activity, while the second discussed types of biosensors that could be used.

However, while Teniou et al. [14] considered a similar research question in their review, they did not focus on how biosensors could be designed to identify IgG in the presence or absence of biomarkers indicating acute infection, such as PCT and lymphocytes or neutrophils.

Karachaliou et al. [15] discussed the overall subject of immunosensors as a subset of biosensors that use specific antibodies to recognize the target analyte. Immunosensors that target disease biomarkers could be leveraged for disease diagnosis and/or follow-up, improving upon current techniques with benefits such as rapid and simple analysis of patients' samples at the point-of-care. While the COVID-19 pandemic has been connected to autoimmunity, autoimmune diseases at large continue to be a global issue. Therefore, this study emphasized immunosensors targeting autoimmune disease biomarkers, primarily various autoantibodies and specific pro-inflammatory proteins (e.g., specific cytokines). This review article proposed these immunosensors to help diagnose conditions such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis.

Notwithstanding, this review did not focus on contrasted recognition of infectious disease biomarkers to help isolate autoimmune activity from acute infection.

In terms of AI used for general biomarker discovery, Javaid et al. [16] reviewed how AI algorithms can be implemented into wearable devices to gather and process data from biomarkers related to autoimmune diseases. Still, they discussed how AI-powered biomarkers have not been easily integrated in a clinical context, due to a lack of population diversity, data harmonization challenges, and time-consuming clinical studies. As a proposed solution, this review introduced the AI toolkit for biomarker discovery. While this use of AI holds promise for the future of AI-equipped biosensing in precision medicine, the applicability of AI and machine learning (ML) to engineering a biosensor capable of isolating autoimmune activity from acute infection was not explored.

In their review, Mobed et al. [17] focused on the advantages of using biosensors to identify abnormal levels of PCT to help detect possible acute bacterial infection, specifically.

This review highlighted various methods of biosensor construction, different immobilization methods, benefits, and roles of different matrices, analytical performance, and PCT biosensor construction. This article also detailed the sensitive limits of detection for these biosensors as well as linearity and other analytical characteristics.

While conventional methods like capillary electrophoresis, high-performance liquid chromatography, and mass spectrometry have been useful to detect PCT in the medical field, they are complex, time-consuming, and costly. In contrast, PCT biosensors present a quick, sensitive, and simple alternative for PCT analysis in various fields, particularly medicine.

Mobed concluded that biosensors could either supplement or replace conventional analytical methods by reducing or streamlining sample preparation to facilitate and expedite, while significantly minimizing the cost per analysis.

However, while Mobed et al. [17] discussed the various advantages of biosensors used to detect PCT in particular, IgG and autoimmunity are not covered.

As autoimmunity can be detected using IgG as a low-grade inflammatory marker, this study examined Wu et al.'s [18] article on noninvasive wearable devices for inflammation monitoring.

Wu began by explaining the convenience and noninvasive nature of wearable technology for inflammation detection. However, an area for improvement includes clinically relevant biofluids. This review discussed the challenges of extracting and identifying analytes in these biofluids. Wu then reviewed three common types of noninvasive wearable biosensors for inflammation monitoring (microneedle patches, flexible electronic skins, and textile-based sensors). The review considered the design and operational needs of these devices, followed by information processing approaches used during data processing.

Similar to Mobed, Wu's review showed a narrow focus, in this case, wearables used specifically for inflammation detection. However, the review did not examine biosensor analysis of autoimmune-related inflammation (such as through IgG) in particular.

Finally, Azam et al. [19] assessed research on biosensor detection of IgG for autoimmunity and viral activity diagnosis. This review covered IgG as a helpful diagnostic tool for many diseases, such as autoimmune hepatitis, hepatitis B virus, chickenpox, MMR (measles, mumps, and rubella), and coronavirus-induced disease 19 (COVID-19). Azam reported that researchers have used various techniques and materials from macro- to nanoscale for IgG biosensing. This review focused on the limitations of these biosensors, particularly electrochemical biosensors that, when combined with nanomaterials, can achieve the capabilities of a proficient IgG biosensor.

Notwithstanding, Azam et al. [19] did not discuss how bacterial biomarkers like PCT and viral biomarkers such as lymphocytes/neutrophils could be analyzed against IgG to help identify the root cause of the immune reaction.

2.3. Literature gap

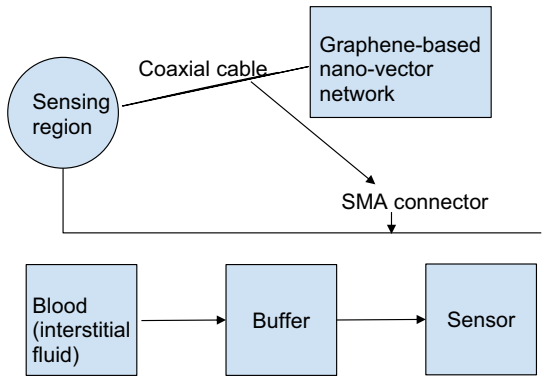
While many studies have explored how wearable technology can be used for biomarker monitoring for inflammation and various types of infection, a research gap remains surrounding wearables for IgG detection in the blood, which could benefit assessment for autoimmune conditions specifically. This biosensing method would be novel in its potential to allow for relatively rapid diagnosis without requiring the wearer to remain still for extended periods of time. The proposed wearable system presented in this article would measure the presence of infection and inflammation within the context of the presence or absence of IgG to help scope out autoimmune activity that could be contributing to a wearer's symptoms.

3. Discussion

3.1. A wearable device solution for isolating autoimmune activity

On the whole, elevated IgG levels were identified as coinciding with baseline or low PCT levels and elevated lymphocytes

Figure 1
IgG differential biosensor design schematic



and neutrophils for isolating bacterial infection and viral infection across all of these studies, respectively. Additionally, multiple studies discussed the role of wearable devices in general biomarker monitoring. However, no studies investigated the potential of wearable devices for identifying and measuring IgG against these other biomarkers, particularly for real-time monitoring.

Helping to isolate autoimmune activity versus active infection could vastly improve the quality of life for those living with such conditions, lending credence to the need for a technology-based metric solution for determining the origin of symptoms.

This physical basis for distress often associated with chronic illness is crucial for preventing over-or misdiagnosis of psychiatric medication in the place of assessing for an underlying physiological condition. This study reviewed existing literature to help determine the frequency with which elevated IgG tends to present in parallel with baseline or low PCT and normal lymphocyte/neutrophil levels in individuals with autoimmune illness. Targeting of excess IgG antibodies through wearable technology could help uncover autoimmune illness for individuals with symptoms previously diagnosed as psychosomatic and otherwise dismissed.

Finally, aspects such as sensor sensitivity, biofluid selection, and calibration must be considered. Sensor sensitivity could be improved by magnifying the signal to decrease noise and improve analyte capture by using nanomaterials (like gold nanoparticles (NPs), quantum dots, or graphene) to boost signals and create 3D nanostructures for more binding sites. Biofluid selection could be weighed between richness and patient comfort, with blood and interstitial fluid being two standard options for those respective qualities [20]. Lastly, the challenge of calibration should be given strong consideration, as maintaining the most accurate and relevant laboratory data might prove elusive for a device set to monitor multiple biomarkers simultaneously.

4. Conclusion

This study has several limitations, including the fact that the sample size of surveyed literature can always be expanded due to the relatively scant research assessing wearable solutions for measuring IgG alongside PCT and lymphocyte/neutrophil levels in patients with suspected autoimmune disease. In addition, classification of low versus high levels for IgG antibodies, PCT, lymphocytes, and neutrophils might vary depending on age and other factors, making those values approximations for the purpose of this study.

Further considerations in this area could include pilot studies with volunteer participants in a teaching hospital or other clinical setting, biosensor material development such as graphene used in existing blood-targeted biosensors, or integration with AI-based data similar to existing data collected from other continuous wearable technology such as continuous glucose monitors (CGMs) [21].

Finally, the Python IgG blood serum metric algorithm designed for the proposed wearable device presented in this study has not yet been validated. As such, clinical trials with real patients are needed to further assess this proposed design. Indeed, issues of wearer comfort and privacy must be further explored, given that the proposed device would measure blood and interstitial fluid [22]. This feature could run the risk of protected health information disclosure and distress due to the continuous monitoring nature of the device.

Recommendations

This review reveals the need for a biosensor designed to monitor for elevated IgG in the absence of infectious disease biomarkers. The schematic in Figure 1 shows the rudimentary design plan for this device, which would use graphene for electrochemical sensing [23].

The following code provides a foundational basis for the wearable device algorithm that identifies IgG antibodies in the presence of baseline or low PCT and normal lymphocytes/neutrophils. This device would generate an alert to notify of possible autoimmune activity for instances of elevated IgG despite low or normal PCT and normal lymphocytes/neutrophils in an individual's blood serum, similar to how an insulin pump measures insulin levels in the blood plasma of individuals with diabetes.

Similar to a CGM, this device could be worn as a patch on multiple regions of the body. Based on IgG monitoring methods for immunodeficiency conditions, this device would be deployed between 1 and 3 months or for as long as 6 months [24]. At a logistical level, the sensor would transmit fluctuations in IgG readings set to a certain increment for the monitoring duration period. This transmission would occur from the subcutaneous fat immediately beneath the first layer of the skin [25].

The following script provides a foundation for assessing abnormal IgG levels against these other biomarkers to help distinguish between autoimmune disease and bacterial infection:

```
# serum_analysis.py

# Reference ranges
IGG_MIN, IGG_MAX = 600, 1600 # mg/dL
PCT_MIN, PCT_MAX = 0.1, 0.5 # ng/mL

def send_alert(title: str, message: str) -> None:
    """Send a desktop notification alert."""
    notification.notify(
        title = title,
        message = message,
        timeout = 8 # seconds
    )
def analyze_levels(igg: float, pct: float) -> str:
    """
    Analyze serum levels of Immunoglobulin G and Procalcitonin.
    """
    if (igg < IGG_MIN or igg > IGG_MAX) and (PCT_MIN
<= pct <= PCT_MAX):
    alert_msg = "Possible autoimmune activity"
    send_alert("Serum Analysis Alert", f "IgG = {igg} mg/dL,
PCT = {pct} ng/mL -> {alert_msg}")
```

```
    return alert_msg
    else:
    return "No alert"

def analyze_csv(file_path: str, output_path: str = "analysis_results.
csv") -> None:
    """
    Analyze multiple serum results from a CSV file.
    CSV file must have columns: 'IgG' and 'PCT'
    """
    if not os.path.exists(file_path):
        raise FileNotFoundError(f "File not found: {file_path}")

    df = pd.read_csv(file_path)

    if "IgG" not in df.columns or "PCT" not in df.columns:
        raise ValueError("CSV must contain 'IgG' and 'PCT'
columns")

    df["Analysis_Result"] = df.apply(lambda row: analyze_levels
(row["IgG"], row["PCT"]), axis = 1)
    df.to_csv(output_path, index = False)
    print(f "Analysis complete. Results saved to {output_path}")

def main():
    if len(sys.argv) == 3 and sys.argv[1] == "–single":
        # Single entry mode
        igg = float(sys.argv[2])
        pct = float(input("Enter Procalcitonin level (ng/mL): "))
        result = analyze_levels(igg, pct)
        print(f"IgG = {igg} mg/dL, PCT = {pct} ng/mL ->
{result}")

    elif len(sys.argv) == 2:
        # Batch mode with CSV
        file_path = sys.argv[1]    analyze_csv(file_path)

    else:
        print("Usage:")
        print(" Single entry: python serum_analysis.py –single
<IgG_value>")
        print(" Batch mode: python serum_analysis.py <path_
to_csv>")
        sys.exit(1)

if __name__ == "__main__":
    main()
```

The following code provides a basis for distinguishing between autoimmune activity and viral infection, using elevated lymphocytes and decreased neutrophils as viral biomarkers:

```
# serum_autoimmune_analysis.py

import pandas as pd
import sys
import os
from plyer import notification # Install with: pip install plyer

# Reference thresholds
IGG_THRESHOLD = 1600 # mg/dL
LYMPHOCYTE_THRESHOLD = 4800 # cells/µL
NEUTROPHIL_THRESHOLD = 1500 # cells/µL

def send_alert(title: str, message: str) -> None:
    """Send a desktop notification alert."""
    notification.notify(
        title = title,
        message = message,
        timeout = 8 # seconds
    )

def analyze_levels(igg: float, lymphocytes: float, neutrophils:
float) -> str:
    """
    Analyze serum levels for possible autoimmune activity.
    """
    if igg > IGG_THRESHOLD and lymphocytes < LYMPH
OCYTE_THRESHOLD and neutrophils > NEUTROPHIL_
THRESHOLD:
        alert_msg = "Possible autoimmune activity"
        alert_details = f"IgG = {igg} mg/dL, Lymphocytes =
{lymphocytes}, Neutrophils = {neutrophils}"
        send_alert("Serum Analysis Alert", f"{alert_msg}\n{
alert_details}")
        return alert_msg
    else:
        return "No alert"

def analyze_csv(file_path: str, output_path: str = "autoimmune_
analysis_results.csv") -> None:
    """
    Analyze multiple patient results from a CSV file.
    CSV file must contain columns: 'IgG', 'Lymphocytes', and
'Neutrophils'.
    """
    if not os.path.exists(file_path):
        raise FileNotFoundError(f "File not found: {file_path}")

    df = pd.read_csv(file_path)

    required_columns = {"IgG", "Lymphocytes", "Neutro
phils"}
    if not required_columns.issubset(df.columns):
        raise ValueError(f "CSV must contain columns: {', '.join
(required_columns)}")

    df ["Analysis_Result"] = df.apply(
        lambda row: analyze_levels(row["IgG"], row["Lympho
cytes"], row["Neutrophils"]), axis = 1
    )

    df.to_csv(output_path, index = False)
    print(f "Analysis complete. Results saved to {output_path}")

def main():
    if len(sys.argv) == 4 and sys.argv[1] == "–single":
        # Single-entry mode
        igg = float(sys.argv[2])
        lymphocytes = float(input("Enter Lymphocyte count
(cells/µL): "))
        neutrophils = float(input("Enter Neutrophil count (cell-
s/µL): "))
        result = analyze_levels(igg, lymphocytes, neutrophils)
        print(f "IgG = {igg} mg/dL, Lymphocytes = {lympho-
cytes}, Neutrophils = {neutrophils} -> {result}")

    elif len(sys.argv) == 2:
        # Batch mode (CSV input)
        file_path = sys.argv[1]
        analyze_csv(file_path)
```

```
    else:
        print("Usage:")
        print(" Single entry: python serum_autoimmune_analysis.
py –single <IgG_value>")
        print(" Batch mode: python serum_autoimmune_analysis.
py <path_to_csv>")
        sys.exit(1)
if __name__ == "__main__":
    main()
```

Acknowledgment

The author is grateful to the faculty at Capitol Technology University and the Rockwell School of Holistic Medicine for providing educational support for this article.

Ethical Statement

This study does not contain any studies with human or animal subjects performed by the author.

Conflicts of Interest

The author declares that she has no conflicts of interest to this work.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contribution Statement

Sarah Katz: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

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How to Cite: Katz, S. (2026). Biosensors for IgG Identification in the Absence of Infection to Isolate Autoimmune Activity. *Smart Wearable Technology*. https://doi.org/10.47852/bonviewSWT62028721