# Case Validation of Cutaneous Lymphomas to Minimize Protopathic Bias

Lia Gutiérrez,[1] Helen Booth,[2] Elizabeth Crellin,[2] Daniel Dedman,[2] Carla Franzoni,[1] James A Kaye,[3] Susana Perez-Gutthann,[1] Alejandro Arana,[1] Marcus Schmitt-Egenolf,[4] Camilla Byström,[5] Anders Sundström[5]

[1]RTI Health Solutions, Barcelona, Spain; [2]Clinical Practice Research Datalink, Medicines and Healthcare products Regulatory Agency, London, United Kingdom; [3]RTI Health Solutions, Waltham, Massachusetts, United States; [4]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [5]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden

## DISCLOSURES

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LG, CF, JAK, SPG, and AA are employees of RTI Health Solutions, a unit of RTI International, a non-profit organization that conducts work for government, public, and private organizations, including pharmaceutical companies. HB, EC, and DD are employees of the Medicines and Healthcare products Regulatory Agency of the United Kingdom. This independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies. MSE is employee of the Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden. CB and AS are employees of the Centre for Pharmacoepidemiology of the Karolinska Institutet in Sweden, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies.

## BACKGROUND

- Protopathic bias in epidemiologic studies may affect study findings when a drug is prescribed to treat symptoms or signs of a study outcome that has not yet been diagnosed, appearing as a reversal of cause and effect.
- Protopathic bias may be of particular concern when studying outcomes with long latencies, such as cancer. It is commonly controlled by including a time lag in sensitivity analyses.
- In a multi-country cohort study of the potential association of topical tacrolimus or topical pimecrolimus with cutaneous lymphoma (CL), protopathic bias was a concern because early stages of CL may present with clinical manifestations resembling atopic dermatitis and therefore study subjects could have been treated with the study medications (Figure 1).

## OBJECTIVE

- To evaluate the potential for protopathic bias by acquiring further information on the medical history of CL cases.
- To assess whether treatment with the study medications was initiated for symptoms or signs that were compatible with early manifestations of CL.

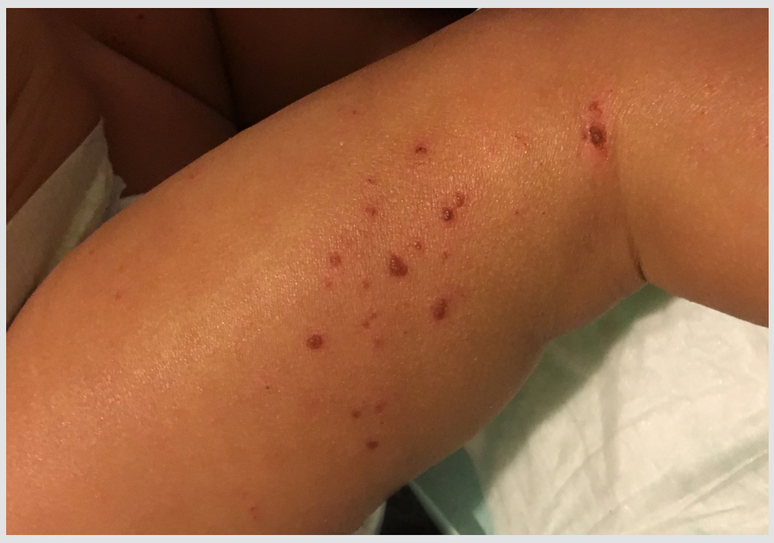
## METHODS

- In the United Kingdom (UK), researchers from the Clinical Practice Research Datalink (CPRD) sent questionnaires to general practitioners (GPs) of potential CL cases identified in primary care, linked hospital, and/or cancer registry data.
- In Sweden, researchers reviewed hospital medical records of potential CL cases identified through the Swedish Cancer Registry.
- Information evaluated included date of CL diagnosis; date of start of symptoms; location and extent of CL; biopsy results; and skin conditions such as psoriasis or atopic dermatitis, including location, extent, and date of onset.

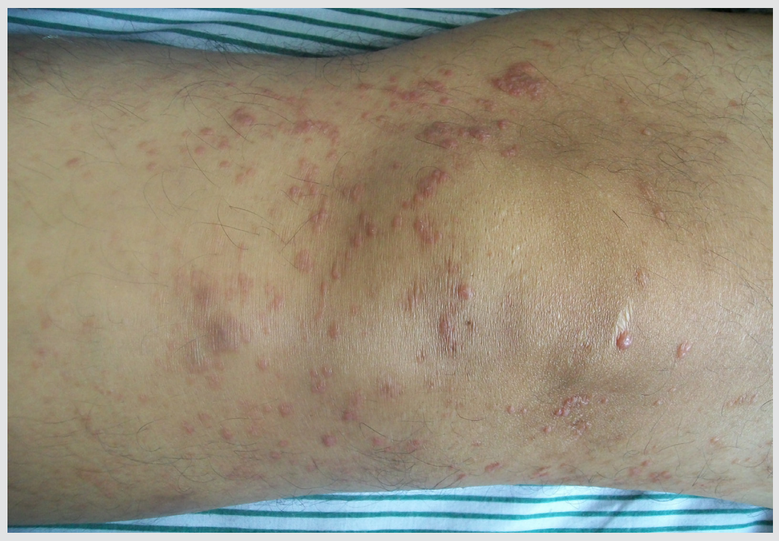
## RESULTS

- In total, 29 (UK) and 65 (Sweden) potential CL cases were identified.
- In the UK, GP questionnaires were sent for all 29 potential cases identified, and 19 were returned.
  - One did not provide additional information.
  - CL diagnosis was confirmed in 13 cases.
    - In 4 cases, the date of CL diagnosis identified by the case screening algorithm was changed by the GP to an earlier date (during patient follow-up).
    - 6 cases had a history of signs or symptoms of a previously diagnosed skin condition in the same location as the CL that was suspicious of protopathic bias, 1 did not, and 6 did not provide enough information for assessment (Figure 2).
- In Sweden, medical records were sought for 65 potential CL cases identified in 63 patients. In 2 patients, the information could not be requested (private clinics or no clinic information available).
  - Among the remaining 61 patients, 53 medical records were retrieved. However, 3 patients had a non-CL diagnosis and were not considered for further review.
  - In total, 50 medical records were reviewed. Diagnosis and date of diagnosis were confirmed in 38 cases.
  - 28 cases had a history of a skin condition in the same location as the CL that was suspicious of protopathic bias, and 10 cases had no previous history of a treated skin condition or did not provide enough information (Figure 2).

**Figure 1. Examples of Atopic Eczema and Mycosis Fungoides**



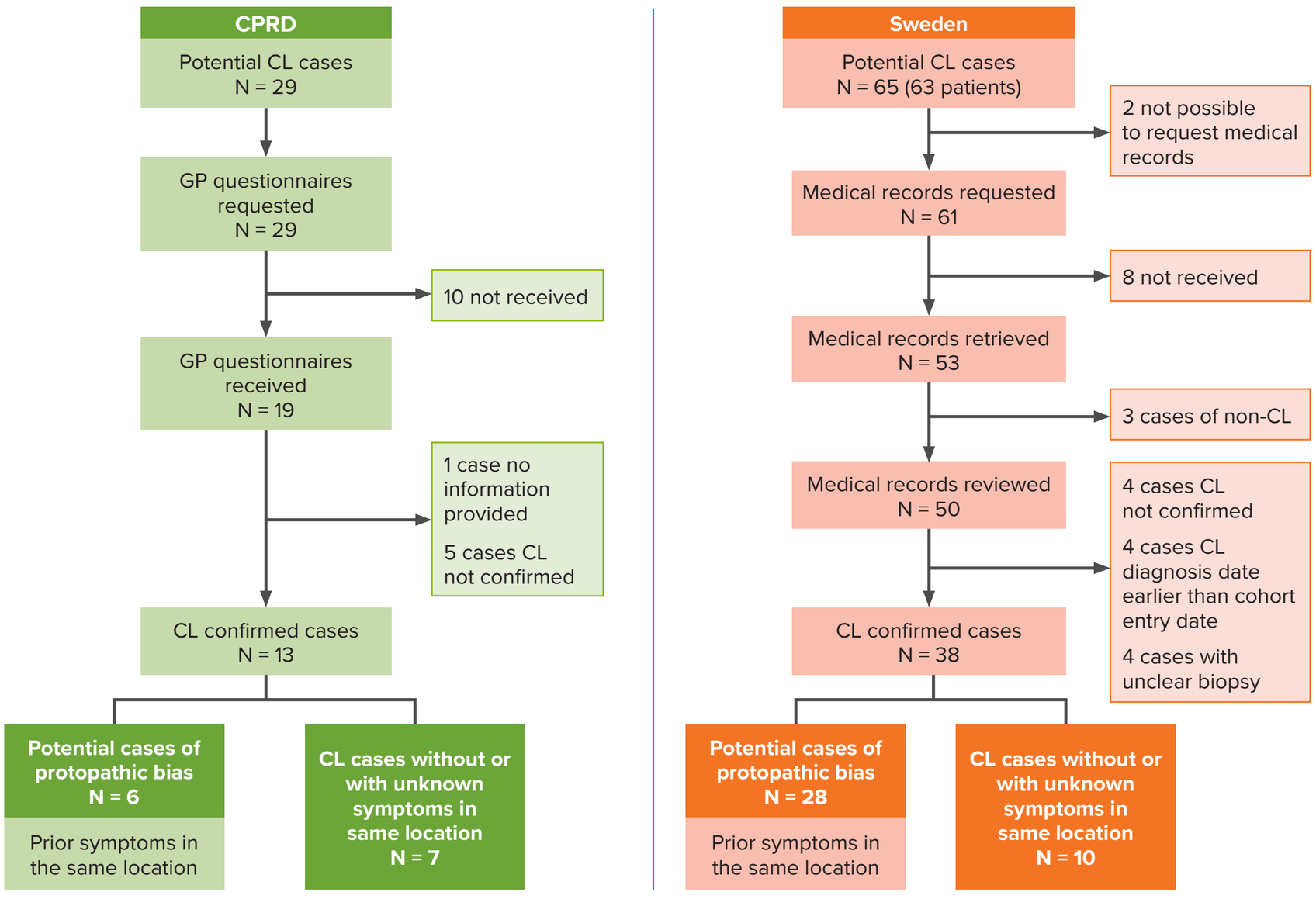
**Childhood atopic eczema**



**Cutaneous T-cell lymphoma**
(early stage mycosis fungoides)

**Similar appearance of childhood atopic eczema (left) and mycosis fungoides (right).** Initial manifestations of CL may resemble those of atopic dermatitis, so cases of eczema may be treated with the study medications (tacrolimus or pimecrolimus), which are intended to treat atopic dermatitis.

**Figure 2. Validation Results in CPRD (UK) and Sweden**




## CONCLUSIONS

- Nearly half of the confirmed cases in the UK and almost 75% of the confirmed cases in Sweden were previously diagnosed with nonmalignant skin conditions that can present with similar signs or symptoms to those of early stages of CL and may represent protopathic bias.
  - This may underestimate the extent of the potential for protopathic bias because cases with insufficient information were not counted here.
- Some patients diagnosed with atopic dermatitis or other cutaneous diseases may, in fact, have been CL cases misdiagnosed as atopic dermatitis and treated as such until the correct diagnosis was made.
- Restricting the analyses of the association of topical tacrolimus and pimecrolimus with CL to cases for which protopathic bias is unlikely may provide further insight about the potential causal relationship between use of the study drugs and the development of CL.

## CONTACT INFORMATION

**Lia Gutiérrez, BSN, MPH**

RTI Health Solutions
Av. Diagonal 605, 9-1
08028, Barcelona, Spain

E-mail: lgutierrez@rti.org



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